A RANDOMIZED, OPEN LABELLED, SINGLE CENTERED STUDY OF METFORMIN IN PREVENTING METABOLIC SYNDROME ASSOCIATED WITH INITIATION OF ATYPICAL ANTIPSYCHOTIC THERAPY IN ADOLESCENTS AND YOUNG ADULTS

DISSERTATION SUBMITTED TO

THE TAMILNADU DR.M.G.R MEDICAL UNIVERSITY

IN PARTIAL FULFILLMENT FOR THE AWARD OF THE DEGREE OF

DOCTOR OF MEDICINE

IN

PHARMACOLOGY

DEPARTMENT OF PHARMACOLOGY

TIRUNELVELI MEDICAL COLLEGE

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BONAFIDE CERTIFICATE

This is to certify that the dissertation entitled **"A RANDOMIZED , OPEN LABELLED , SINGLE CENTERED STUDY OF METFORMIN IN PREVENTING METABOLIC SYNDROME ASSOCIATED WITH INITIATION OF ATYPICAL ANTIPSYCHOTIC THERAPY IN ADOLESCENTS AND YOUNG ADULTS"** submitted by **Dr.R.VISHNUPRIYA** to the Tamilnadu Dr. M.G.R Medical University, Chennai, in partial fulfillment of the requirement for the award of the Degree of Doctor of Medicine in Pharmacology during the academic period 2012 - 2015 is a bonafide research work carried out by her under direct supervision & guidance.

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DECLARATION

I, **Dr.R.VISHNUPRIYA** declare that, I carried out this work on **"A RANDOMIZED ,OPEN LABELLED , SINGLE CENTERED STUDY OF METFORMIN IN PREVENTING METABOLIC SYNDROME ASSOCIATED WITH INITIATION OF ATYPICAL ANTIPSYCHOTIC THERAPY IN ADOLESCENTS AND YOUNG ADULTS"** at the Department of Pharmacology, Tirunelveli Medical College and I also declare that this bonafide work or a part of this work was not submitted by me or any others for any award, degree, or diploma to any other University, Board, either in India or abroad.

This is submitted to the Tamilnadu Dr.M.G.R. Medical University, Chennai in partial fulfillment of the rules and regulations for the M.D Degree examination in Pharmacology.

Place: Tirunelveli

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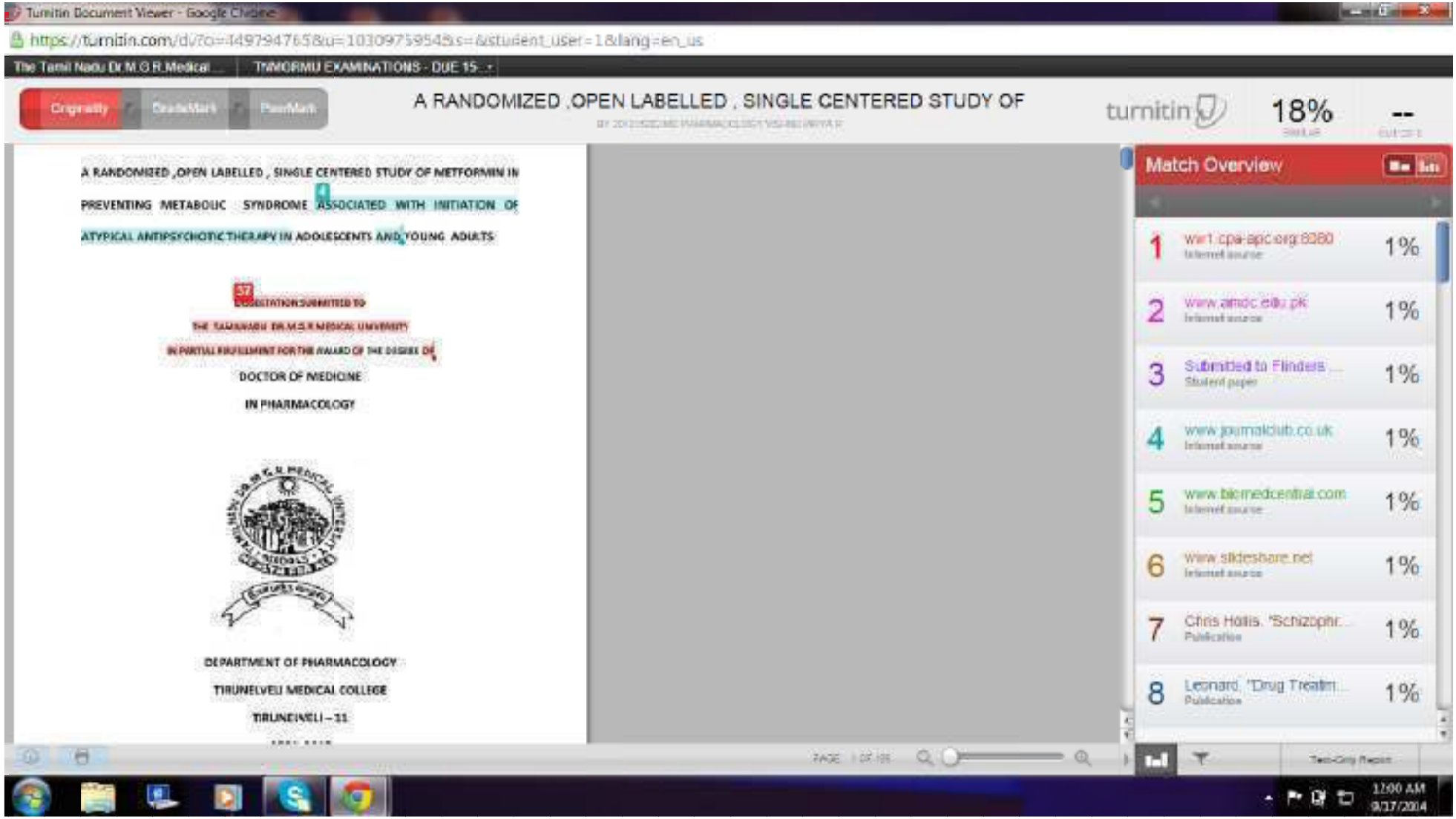
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CONTENTS

A RANDOMIZED ,OPEN LABELLED , SINGLE CENTERED STUDY OF METFORMIN IN PREVENTING METABOLIC SYNDROME ASSOCIATED WITH INITIATION OF ATYPICAL ANTIPSYCHOTIC THERAPY IN ADOLESCENTS AND YOUNG ADULTS

Background:

Schizophrenia is a debilitating brain disorder characterized by a chronic remitting and relapsing course of psychosis that is superimposed on persistent "deficit" features such as negative symptoms and cognitive dysfunction. Metformin is a member of biguanide class of oral hypoglycemic agents. It has been tried for the prevention of metabolic syndrome associated with the use of atypical antipsychotics.

Objective:

The purpose of the study was to evaluate the effectiveness and safety of Metformin along with Risperidone to prevent antipsychotic-induced metabolic syndrome in first episode schizophrenia patients.

Methods:

A randomized,open labelled,prospective study was conducted in the Department of psychiatry,Tirunelveli medical college from March 2013 to February 2014. Around 96 patients with 18 to 40 years of age who have been diagnosed with first episode schizophrenia based on DSM - IV criteria and on treatment with T.Risperidone 2 mg twice a day for $\leq$ 2 months were enrolled for the study.They were randomized into 2 groups. Group1patients were given T. Risperidone (2 mg twice daily,n=48) and group2 Patients were given T.Metformin (500 mg twice daily,n=48) along with T.Risperidone for 6 months.

The primary endpoint assessed was the proportion of patients developing metabolic syndrome at the end of 6 months in both the groups.The secondary

endpoints were the changes in bodymass index,waist circumference,fasting blood sugar and triglycerides from baseline to the end point and the proportion of patients progressing a stage higher from the baseline in terms of BMI at the end of 3 months.

Results:

Baseline characteristics were similar in both the groups ($p>0.05$) except that the patients in group II had higher BMI levels($p < 0.001$) and larger waist circumference levels($p = 0.04$).Of the 48 patients in group I,10 patients developed metabolic syndrome and of the 48 patients in group II,only 1 patient developed metabolic syndrome.There was a significant reduction in BMI and waist circumference at the end of 3 months ($p < 0.001$) and at the end of 6 months ($p < 0.001$) when compared to baseline in group II individuals .

There is significant reduction in FBS and Triglyceride levels at the end of 6 months of treatment($p < 0.001$) in group II individuals.When compared to group I,significantly lesser proportion of patients in group II progressed to the next stage in terms of BMI,3 months after treatment.There was significant statistical difference between both the groups ($p<0.05$) in terms of BMI,WC,FBS,triglycerides. The treatment emergent adverse effects with Metformin was generally mild and did not lead to any discontinuation.

Conclusion:

The use of Metformin along with Risperidone was safe and effective in the prevention of metabolic syndrome induced by atypical antipsychotics. This may have a good impact on the long term cardiovascular morbidity and mortality of the schizophrenia patients .

Keywords:

Schizophrenia, Metabolic syndrome, Atypical antipsychotics, Body mass index, Waist circumference, Fasting blood sugar, Triglycerides.

Introduction:

Schizophrenia is a debilitating brain disorder characterized by a chronic remitting and relapsing course of psychosis that is superimposed on persistent "deficit" features such as negative symptoms and cognitive dysfunction [1]. It has a worldwide prevalence [2] of 1 % and is considered the prototypic disorder for understanding the phenomenology of psychosis [3]. It is associated with a high morbidity and mortality resulting from strikingly high suicide rate of 10 % [4].

The introduction of Chlorpromazine in the late 1950s transformed and formed a new frontier in the clinical management of Schizophrenia. Initially, "conventional neuroleptics" were developed during that era and they were found to effectively control and improve the disease symptomatology but were also associated with major drawbacks that include parkinsonian like movement disorders. As a result of these side effects , newer neuroleptics (termed "atypical antipsychotics") were introduced into clinical use[4]. Although the concerns over extrapyramidal side effects and tardive dyskinesia are less with these group of drugs , there has been a co-occurence of atherogenic dyslipidemia with abdominal adiposity, impaired fasting glucose, insulin resistance or overt Diabetes Mellitus, and Hypertension

that constitutes the cluster of clinical features known as the Metabolic syndrome [1].

Risperidone which comes under the group of atypical antipsychotics is a benzisoxazole derivative[5]. According to CATIE study, 14% of patients receiving Risperidone had been found to have more than 7% increase in weight from baseline[1] . Also a meta analysis by Allison and coworkers has estimated that the mean increase in weight with Risperidone to be 2.1 kg[6]. It has been assumed that increased appetite and central Histamine H_1 antagonism along with alteration of insulin sensitivity and direct impairment of metabolic dysregulation might be the underlying cause for weight gain[7] .These metabolic derangements not only affect the compliance but inevitably also are associated with substantial morbidity (Cardiovasular disease, Hypertension and Diabetes) and mortality [8].

Lifestyle changes are found to be the safe and effective means of controlling weight in patients taking these drugs . However, these sort of behaviour and dietary modifications are difficult to be instituted in subjects with neuropsychiatric disorders [9].

Metformin, member of Biguanide class of Oral hypoglycemic agents increases storage of glycogen in skeletal muscles, lower rates of production of hepatic glucose, increases sensitivity of insulin thereby

reducing blood glucose levels[10]. In view of stemming down the metabolic derangements due to atypical antipsychotics and also due to the paucity of studies using Metformin along with Risperidone in our population, the present study has been designed to evaluate the effectiveness and safety of Metformin along with Risperidone in preventing antipsychotic - induced Metabolic syndrome in first episode schizophrenia patients.

REVIEW OF LITERATURE:

Schizophrenia is one of the most debilitating and most puzzling of psychiatric syndromes. It is described as disordered cognition, including a "gain of - function" in psychotic symptoms and a "loss of - function" in specific cognitive functions , such as working and declarative memory but the characteristic finding of classical neurodegenerative disorders namely progressive dementia is absent [6].

HISTORY:

- ✓ Historically, in the most ancient document in Ayurveda, written about 33 centuries ago, Charaka has described the patient with schizophrenia like illness as one "who is gluttonous, filthy, walks naked, has lost his memory and moves about in an uneasy manner ".
- ✓ 1808 - Haslam clearly described the syndrome clearly.
- ✓ 1860 - However Morel is generally credited for his description of " Demence precoce "
- ✓ 1896 - Emil kraeplin formed the concept of "dementia precox" referring to mental deterioration starting early in life[6].
- ✓ 1911 - Eugen Bleuler coined the term " Schizophrenia ". He described the four primary symptoms - Autism, Ambivalence, loosening of association and Affective flattening .

- ✓ Later half of 20th century - Kurt Schneider described 11 symptoms whose presence in the absence of coarse brain disease was diagnostic of Schizophrenia [11].

MODERN DIAGNOSTIC CRITERIA :

1. First rank symptoms have stood the test of time. These symptoms are featured predominantly in the Diagnostic and Statistical Manual of Mental disorders (DSM) as well as International Classification of Diseases (ICD) of World Health Organization.
2. International Pilot Study of Schizophrenia sponsored by World Health organization was the later ground breaking study for the adoption of explicit ground breaking criteria, which showed Schizophrenia manifested itself in similar ways across very diverse cultures .
3. The creation of the Research Diagnostic criteria (RDC) in 1978 was the next major step towards the current diagnostic criteria which emphasizes on the temporal length of observable psychopathology and differentiation based on the presence or absence of mood symptoms [6].

CURRENT DIAGNOSTIC CRITERIA :

Diagnostic and Stastitical manual of Mental disorders (DSM -IV) and International Classification of Diseases (ICD - 10) are the current versions in use now for the diagnosis of Schizophrenia [6].

TABLE : 1

MAJOR DIAGNOSTIC CRITERIA

	DSM - IV	**ICD-10**
Characteristic symptoms One or more for one Month	1. Bizarre delusions 2.Commenting voices (or) voices conversing	1 . Thought echo / Insertion/ Withdrawal/ Broadcasting 2.Delusions of control 3.Hallucinatory voices 4. Persistent delusions
Two (or) more	1. Delusions 2. Hallucinations 3.Disorganized speech 4.Grossly disorganized (or) catatonic behaviour 5.Negative symptoms	1. Persistent Hallucinations 2.Thought block / Thought disorder 3. Catatonia 4. Negative symptoms 5.Significant personality Change

Time course	One month (Significant proportion) For symptoms listed Plus 6 months social/ Occupational disturbance	One month (Most of the time)
Exclusions	Schizoaffective disorder (or) brief mood disturbance, Direct effect Of drugs of abuse / Medication (or) general Medical condition	Extensive depressive / Manic symptoms (or) Diagnosis of schizoaffective disorder, Overt brain disease; Drug intoxication / Withdrawal

EPIDEMIOLOGY:

Schizophrenia constitutes a serious public health problem all over the world . It is a disorder of relatively high point prevalence, low incidence and high disability[11]. DALY rate of Schizophrenia in Indonesia is higher (321.870) with India at rank 47 (268.903) and the least in Australia (164.255) [12].

Prevalence:

Developed countries show point prevalence in the range of 2.4 to 6.7 per 1000 population at risk . The developing countries show

prevalence in the range of 1.4 to 6.8 per 1000 population at risk [6]. Estimates of China are observed to be lower than the other third world countries .The point prevalence rates are uniformly low at 1.8/1000[13]. In Chennai, the prevalence rate of schizophrenia was 2.62/1000 [14].

Incidence:

Hafner et al [15] and Eaton et al [16] have suggested that Ireland , Germany and United states show higher incidence rates (Range 0.5 - 0.7/1000) compared to Scandinavia and England (Range 0.1 - 0.2 /1000) . India reports higher incidence rates compared to West . West Bengal[17], Chandigarh [18] and Chennai [19] report significant cases in India.

According to a community survey , incidence rates in West Bengal were found to be 0.93/1000. Chandigarh reports an incidence rate of 0.38/1000 in urban areas and 0.44/1000 in rural areas and the rate in Chennai was found to be 0.35/1000.

Gender:

Schizophrenia was found equally prevalent in men and women . The onset of schizophrenia before 10 years and 60 years of age was extremely rare . For men, peak age of onset was 10 to 25 years and for women, it was 25 - 35 years [20].

Illness:

Several studies have suggested that 80% of patients with schizophrenia have significant concurrent medical illnesses. Around 50 percent of patients remain undiagnosed. Risk of hospitalization is increased with alcohol abuse [20].

ETIOLOGY [23]:

The exact etiology of Schizophrenia is currently unknown. However several theories have been proposed; these include the following.

I . BIOLOGICAL THEORIES

a) Genetic hypothesis

b) Biochemical theories

c) Neuropathology

d) Neuroanatomy

II . PSYCHOLOGICAL THEORIES

a) Stress vulnerability hypothesis

b) Psychoanalytical theories

III . PRENATAL AND PERINATAL INSULT

IV. FAMILY DYNAMICS

I . BIOLOGICAL THEORIES :

a) Genetic hypothesis:

Rather than being the result of a single gene defect, mutations (or) polymorphisms of many genes appear to contribute to the risk for schizophrenia[3]. Implicated are genes that regulate synaptic DA availability (Val{108/158} Met polymorphism of catechol - O - methyl transferase, neuronal migration, synaptogenesis (neuregulin 1), (dystrobrevin binding protein 1 or dysbindin, particularly with schizophrenia patients with prominent negative symptoms), nicotinic neurotransmission (Alpha 7 - receptor polymorphisms) and cognition (disrupted - in - schizophrenia -1) [21].

Increased rates of genome - wide DNA micro duplications termed copy number variants are reported in Schizophrenia patients[22]. Epigenetic changes, including disruptions in DNA methylation patterns are noted in various brain regions[21]. However, this biological disposition alone may not be sufficient to cause Schizophrenia but they probably require certain trigger such as exposure to prenatal insults. This is known as the **Diathesis - stress theory of illness** and has been an influential etiological model for atleast 20 years[24] .

Family, Twin, Adoption studies :

Family studies:

Family studies suggest that the magnitude of the increased risk varies not with the amount of sharing of experience but with the amount of sharing of genes. Identical twins and off springs of dual matings have greater risks than the first degree relatives . The basic risk of schizophrenia is 1 percent in the population[25, 26].

Twin studies :

Twin studies provide a strong evidence that Schizophrenia is heritable . However, because monozygotic twins are far from being 100 % concordant for illness (Concordance rates are roughly 48 % for monozygotic twins and 17 % for dizygotic twins), genetics can only be the part of the explanation . Involvement of other factors is also clear [25,26].

Adoption studies :

The first adoption study conducted by Heston suggested that 10.4 % of the 47 adopted away off springs of Schizophrenia mothers were themselves Schizophrenic compared to none of the 50 adopted away offspring of matched normal mothers .

In an important study, Tiennari and colleagues followed a sample of Finnish adults who had been born to mothers with

Schizophrenia and then adopted at early stages . It was found that even though there was little or no Schizophrenia in the adoptive rearing families , the at - risk children later developed significantly higher levels of psychosis than found in similarly adopted offspring of normal parents [27,28] .

In summary, the preceding family , twin and adoption studies have made a solid case for the genetic etiology of Schizophrenia within diathesis - stress model [24].

b) Biochemical theories :

- Severity of positive psychotic symptoms in Schizophrenic patients has been due to the excessive dopamine release **(Dopamine hypothesis**).
- Also, both the positive and the negative symptoms in Schizophrenia has been thought to be caused by increased Serotonin levels (**Serotonin hypothesis) .**
- Schizophrenia results from diminished inhibitory influences on neuronal function which may be due to the hypo functioning of NMDA receptors located on GABA ergic inter neurons **(Glutamate hypothesis**) [29] .
- Reduced amounts of nicotinic and muscarinic receptors have been demonstrated in the Caudate - Putamen , Hippocampus and

selected regions of Prefrontal cortex in the post mortem studies done in Schizophrenia patients .

- ❖ Loss of GABA ergic neurons in Hippocampus are also revealed in some patients with Schizophrenia .
- ❖ Anhedonia associated with Schizophrenia may be due to the selective neuronal degeneration within the nor epinephrine reward neural system [20] .

c) Neuropathology :

- ❖ CT scans of Schizophrenia patients have consistently revealed enlargement of lateral and third ventricles and cortical volume reduction .
- ❖ Reduction in symmetry has been reported in several brain areas including temporal , frontal and occipital lobes.
- ❖ Within the Hippocampus , neurons were found disorganized. As Cerebellum and Basal ganglia are involved in the control of movements, these areas are thought to be involved in the patho physiology of Schizophrenia .
- ❖ Positron Emission Tomography (PET) scan shows hypofrontality and reduced glucose utilisation in the dominant temporal lobe. It is also hypothesized that disturbances in prefrontal and limbic system function may result from an early developmental lesion of the dopaminergic tracts to the prefrontal cortex . This in turn

leads to cognitive impairments and positive and negative symptoms in Schizophrenia patients.

- Studies using Magnetic Resonance Spectroscopy has revealed that Schizophrenia patients had increased levels of Phospho di esters and lower levels of Phospho mono esters and inorganic phosphate than the control group. Also, N - acetyl aspartate concentrations (marker of neurons in Hippocampus and frontal lobes) were lower in Schizophrenia patients [20].

D) Neuroanatomy :

The symptoms of Schizophrenia , the therapeutic effects as well as side effects of anti psychotic effects can be explained by the neuroanatomy of dopamine neuronal pathways in the brain .

1) Nigrostriatal dopamine pathway :

This pathway connects Substantia nigra to the basal ganglia or striatum, which is a part of the extrapyramidal nervous system that controls motor function and movement .

2) Mesolimbic dopamine pathway :

This pathway projects from the midbrain ventral tegmental area to the nucleus accumbens.This pathway is found to be involved in hallucinations and delusions in psychosis.

3) Mesocortical dopamine pathway :

It is a pathway related to mesolimbic dopamine pathway. It also projects from the midbrain ventral tegmental area but sends its axons to areas of the prefrontal cortex. They may have a role in mediating affective symptoms (ventromedial prefrontal cortex, VMPFC) and cognitive symptoms (dorsolateral prefrontal cortex, DLPFC) of Schizophrenia .

4) Tubero infundibular dopamine pathway :

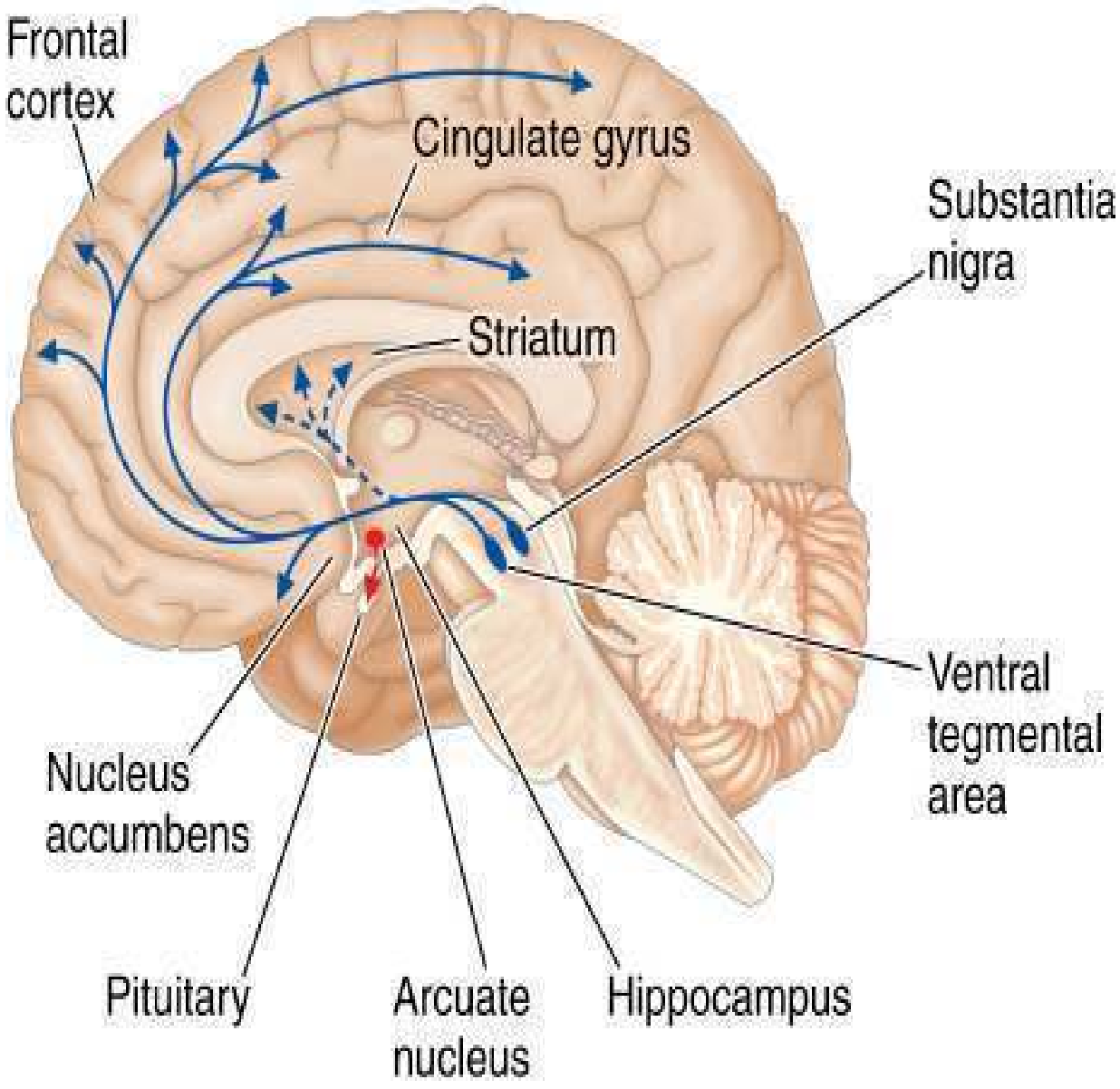
It is the fourth dopamine pathway of interest which projects from the hypothalamus to the anterior pituitary gland and controls prolactin secretion .

5) The fifth dopamine pathway :

This pathway arises from multiple sites including periaqueductal gray, ventral mesencephalon, hypothalamic nuclei and lateral parabrachial nucleus, and it projects to the thalamus. Its function is not currently well known[30] .

FIG 1

DOPAMINERGIC PATHWAYS IN BRAIN



I . PSYCHOLOGICAL THEORIES

a) Stress vulnerability hypothesis

A genetically vulnerable person develop Schizophrenia with increased number of stressful life events before the onset (or) relapse . According to this hypothesis, higher the genetic vulnerability in a person , lesser the environmental stress needed to precipitate a relapse .

b) Psychoanalytical theories :

Sigmund Freud postulated that the fixations that occured during the development resulted in Schizophrenia. Freud postulated that the symptoms of Schizophrenia were due to such defects [23].

III . PRENATAL AND PERINATAL INSULT :

- Exposure to a teratogen during gestation
- Any complications during labour or delivery
- Fetal hypoxia
- Maternal viral infections
- Prenatal nutritional deficiency

Any of the above causes may predispose to Schizophrenia [24].

IV . FAMILY DYNAMICS :

Any of the below causes makes the families vulnerable to Schizophrenia

- Prominent schism between the parents , one parent overly close to a child of opposite sex

- Skewed relationship between one parent and child
- Pseudomutual and pseudohostile verbal communication within families
- Increased levels of expressed emotions in families [20].

MODE OF TRANSMISSION :

Single gene model and the multifactorial (Polygenic) model are the two types of transmission most frequently hypothesized . According to single gene model, even if gene is present , it may not be fully expressed clinically (ie, not everyone who has the gene will get the disease) [24].

Gottesman introduced the alternative polygenic multifactorial threshold model into the field of Schizophrenia . According to this model, a complex illness such as Schizophrenia is the result of the interaction of several small genes as well as other factors either environmental or biological [25].

CLINICAL FEATURES :

Schizophrenia is characterized by psychotic symptoms as follows.

1 . Hallucinations :

The most common type of hallucination in Schizophrenia are auditory hallucinations.

2 . Delusions :

Paranoid delusions, Delusions of reference (or) Delusions of control are more common in Schizophrenia .

3 . Passivity phenomena :

These include thought broadcast, thought insertion and thought withdrawal .

4 . Disordered thought and speech :

This may present as neologisms, incoherency in speech (or) paucity of ideas and content .

5 . Reduced or inappropriate emotional reactivity and lack of volition:

Schizophrenia patients have incongruous emotions, flattened affect, lack of initiation and drive .

6 . Motor abnormalities :

These phenomena may include posturing, mannerisms and catatonic immobility .

Symptoms in Schizophrenia can be seen as representing either an excess of normal function (positive symptoms) or loss (or) reduction of normal function (negative symptoms) [31].

Positive symptoms - passivity phenomena, hallucinations, delusions, thought disorder, disorganized behaviour .

Negative symptoms - Blunted speech, poverty of speech and thought , withdrawal and impaired volition .

Apart from positive and negative symptoms, numerous studies also include cognitive symptoms, aggressive symptoms and affective symptoms into the diagnostic criteria [30].

Aggressive symptoms such as frame violence, verbally abusive behaviours and assaulting nature can occur with positive symptoms and can be confused with positive symptoms .

Cognitive symptoms :

- Problems in representing and maintaining the goals
- Problems in focussing and sustaining attention
- Problems in evaluating the functions
- Problems in monitoring the performance
- Problems in priority making
- Problems with serial learning
- Impaired verbal fluency
- Difficulty in problem solving

It can also be difficult to separate the symptoms of formal cognitive dysfunction from the negative symptoms and from the symptoms of affective dysfunction. But various researches are being attempted to localize the specific areas of brain dysfunction for each

symptom domain in Schizophrenia with the hope of developing treatments for the often - neglected negative, cognitive and affective symptoms of Schizophrenia. In particular, neuropsychological assessment batteries are being developed to quantify cognitive symptoms, in order to detect cognitive improvement after treatment with a number of novel psychotropic drugs currently being tested [30] .

LOCALIZATION OF SYMPTOM DOMAINS :

The different symptom domains of Schizophrenia are hypothesized to be regulated by unique brain regions .

- ✓ Positive symptoms of Schizophrenia are hypothetically modulated by malfunctioning mesolimbic circuits.
- ✓ Negative symptoms are hypothetically linked to malfunctioning mesocortical circuits and may also involve mesolimbic regions such as the nucleus accumbens which is a part of brain's reward circuitry and thus plays a role in motivation . Nucleus accumbens may also be involved in the increased rate of substance use and abuse seen in patients with Schizophrenia .
- ✓ Affective symptoms are associated with the ventromedial prefrontal cortex.
- ✓ Aggressive symptoms are associated with abnormal processing of information in amygdala and the orbito frontal cortex .

- ✓ Cognitive symptoms are associated with problematic information processing in the dorso lateral prefrontal cortex.

Although there is an overlap in function among different brain regions, understanding the brain regions predominantly involved in specific symptoms can aid in the customization of treatment to particular symptom profile of each individual patient with Schizophrenia [30] .

DIAGNOSTIC SUBTYPES :

Schizophrenia can be classified into several subtypes.

Paranoid Schizophrenia :

The characteristic feature of Paranoid Schizophrenia is the presence of frequent auditory hallucinations and either one or more delusions . No prominent disturbances of affect, volition, speech, and / or motor behaviour.

Disorganized (or) Hebephrenic type :

The term Hebephrenia was first described by Ewald Hecker. The characteristic features of this subtype are incoherence , thought disorder and severe loosening of association. Presence of insidious onset, continuous course, poor premorbid function and a poor prognosis are the distinctive features of this subtype.

Catatonic type :

The criteria for the catatonic subtype requires two to five of the following characteristic symptoms .

- Immobility [(Stupor) or (catalepsy)]
- Excessive purposeless motor activity
- Negativity
- Peculiar movements [Posturing , stereotypies , mannerisms , (or) grimacing]
- Echolalia (or) echopraxia

Undifferentiated type :

This category is defined to include patients who meet the criteria for Schizophrenia but cannot be clearly classified. The diagnosis of this subtype is through the exclusion of other subtypes .

Residual type :

This diagnostic criteria is used for patients who have had atleast one psychotic episode in the past and have met the criteria for schizophrenia before but no longer have psychotic symptoms .

Simple type (Simple deteriorative disorder) :

This category is not included in DSM - IV - TR criteria but still exists in ICD - 10 criteria. The diagnosis is solely based on deficit (or) negative symptoms. Psychotic symptoms are not necessary for the diagnosis.

The catatonic and hebephrenic subtypes of Schizophrenia together have been called as nuclear Schizophrenia as they present with typical symptomatology of Schizophrenia and can most frequently result in personality deterioration over time (especially if chronic)[11].

Other subtypes [20] :

Bouffee Delirante (Acute delusional psychosis)

- Latent
- Oneiroid
- Paraphrenia
- Pseudoneurotic Schizophrenia
- Post psychotic depressive disorder of Schizophrenia
- Early onset Schizophrenia
- Late onset Schizophrenia
- Deficit Schizophrenia

COURSE AND PROGNOSIS :

Course :

The classical course of Schizophrenia consists of remissions and exacerbations . A patient recovers and functions normally after the first psychotic episode but the patients usually relapse. The patient's baseline functioning deteriorates after every episode of psychosis. Vulnerability to stress is lifelong in patients with schizophrenia. Positive symptoms

become less severe with time. However the negative or symptoms increase in severity [31].

Prognosis :

- Only about 10 to 20 % of patients have a good outcome after the first psychiatric hospitalization for Schizophrenia .
- More than 50 % of patients have a poor outcome such as symptom exacerbation, repeated hospitalization and suicide attempts .
- About 40 to 60 % of patients remain impaired by the disorder throughout the life and 20 to 30% of patients continue to experience symptoms moderately [31] .

TABLE 2

PROGNOSIS

Good prognosis	Bad prognosis
Late onset	Young onset
Obvious precipitating factors	No precipitating factors
Married	Single/divorced/widowed
Good support systems	Poor support systems
Positive symptoms	Negative symptoms

DIFFERENTIAL DIAGNOSIS [31] :

- ✓ Organic mental disorders with Schizophrenia - like symptoms may be seen in Huntington's chorea (early stage), omocystinuria , Acute intermittent porphyria, Wilson's disease, Haemochromatosis
- ✓ Secondary psychotic disorders
- ✓ Other psychotic disorder
    - Schizophreniform disorder
    - Brief psychotic disorder
    - Schizo affective disorder
    - Delusional disorder
- ✓ Mood disorders
    - Unipolar
    - Bipolar
- ✓ Personality disorders
    - Schizotypal
    - Schizoid
    - Borderline personality disorder
- ✓ Malingering
- ✓ Factitious disorders .

DIAGNOSIS :

Diagnosis [20] is mainly by

I) Mental status examination

II) Certain psychological tests

- Halstead - Reitan battery
- Luria - Nebraska battery

III) Intelligent tests

IV) Projective tests

- Rorschach test
- Thermatic appreciation test

V) Personality tests

- Minnesota Multiphasic Personality Inventory

MANAGEMENT:

Management of Schizophrenia includes pharmacological, physical methods [11] and psychosocial interventions [20] .

1) Pharmacotherapy :

This includes typical and atypical antipsychotics .

2) Physical methods :

- Electroconvulsive therapy
- Psychosurgery

3) Psychosocial interventions :

- Social skills training

- Family oriented therapy
- Cognitive behavioral therapy
- Vocational therapy

I . PHARMACOTHERAPY :

The drugs currently used to treat Schizophrenia are classified as either typical (also referred to as first generation) (or) atypical (second generation) antipsychotics.

Typical antipsychotics :

Henri Laborit , surgeon in Paris , in the early 1950 's discovered the " calming " effect of Chlorpromazine in Schizophrenia patients .

In 1963, Carlsson and Linquist found an association between the Phenothiazine's therapeutic effect and dopamine inhibition. This resulted in the dopamine hypothesis of Schizophrenia. It postulated that psychosis was due to an increase in dopaminergic function in the brain . Neuroleptics alleviate the symptoms of schizophrenia by blocking the dopamine receptors .

During the late 1970's, it was shown that the action of neuroleptics was better correlated with their effect of blocking the dopamine receptors in vitro .

In 1979, Kebabian and Calne classified dopamine receptors into two specific types and correlated the potency of Phenothiazine neuroleptics and Haloperidol and their affinity for D_2 receptors .

After the introduction of molecular cloning techniques, five distinct subtypes of the dopamine receptor have been discovered and they are broadly classified into those resembling the original D_1 receptor (D_1 & D_5) and those resembling the D_2 receptor (D_2, D_3 & D_4) [32] .

CLASSIFICATION (TYPICAL ANTIPSYCHOTICS) :

A) Phenothiazines :

- **Aliphatic derivative** : Chlorpromazine , Trifluopromazine
- **Piperidine derivative** : Thioridazine .
- **Piperazine derivative**: Perphenazine, Fluphenazine, Thioproperazine

B) Butyrophenones :

Haloperidol , Trifluperidol , Droperidol , Penfluridol .

c) Thioxanthines :

Chlorprothixine , Thiothixine , Flupenthixol .

d) Miscellaneous :

Pimozide , Molindone , Loxapine [3] .

Typical antipsychotics have potent dopamine D_2 receptor blocking property and to a lesser extent , 5 - HT receptor blockade. They are also called neuroleptic drugs. Phenothiazines and Thioxanthines also block D_1 , D_3 & D_4 receptors.

Blockade of dopamine receptors ,

- In the limbic system leads to antipsychotic effect .
- In the CTZ leads to antiemetic effect .
- In the corpus striatum leads to extrapyramidal side effects.
- including Parkinson 's disease .
- In the anterior pituitary leads to increased prolactin level i.e,
- Hyperprolactinaemia .

High efficacy (low dose) neuroleptics such as Haloperidol , Fluphenazine and Trifluoperazine with more specific action cause EPS more often . This is because the low dose neuroleptics are more selective in binding to D_2 receptors .

Low efficacy (high dose) drugs such as Chlorpromazine have high affinities for H_1 , M_1 , and α_1 receptors that cause many undesirable effects (sedation , anticholinergic properties , orthostasis) but have lesser chances of EPS [33] .

ATYPICAL ANTIPSYCHOTICS :

An important breakthrough occured in the development of novel neuroleptics 25 years ago. Clozapine was discovered and it was novel because it caused attenuation of both the positive and negative symptoms of Schizophrenia without causing EPS (or) elevating serum prolactin concentrations [32].

CLASSIFICATION (ATYPICAL ANTIPSYCHOTICS) :

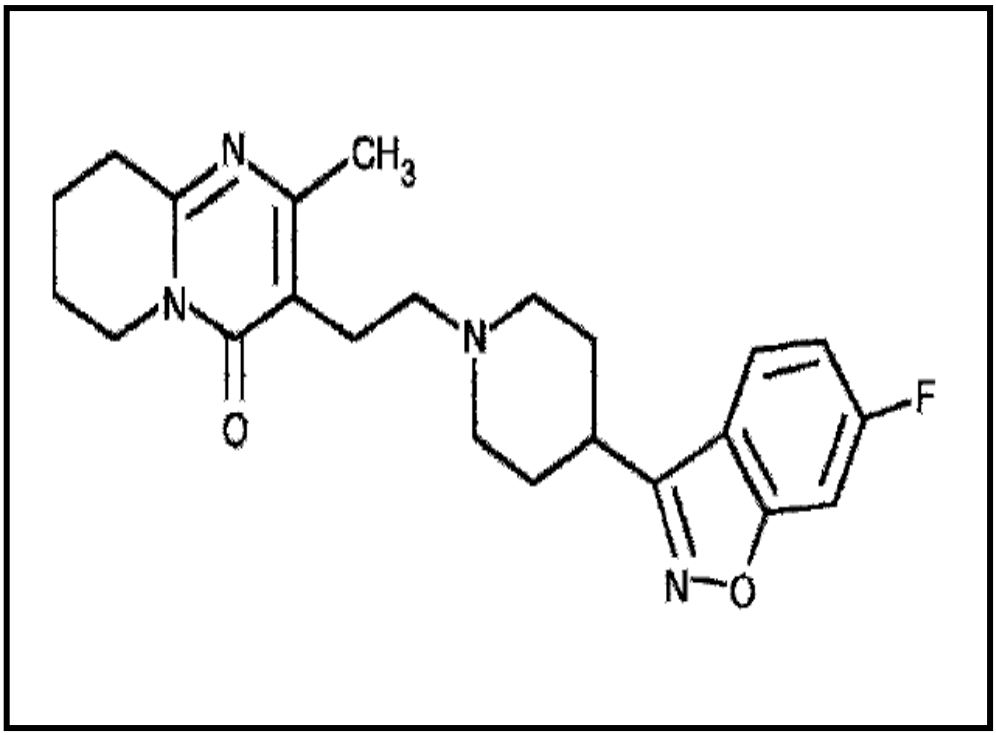
- **Dibenzodiazepines** : Clozapine .
- **Thienobenzodiazepines** : Olanzapine .
- **Dibenzothiazepines** : Quetiapine .
- **Benzamide** : Sulpiride , Amisulpiride .
- **Benzisoxazole** : Risperidone .
- **Indole derivative** : Sertindole .
- **Others** : Aripiprazole , Ziprasidone , Asenapine [3] .

These drugs block 5 - HT_{2A} receptors more than D_2 receptors [29]. They also act as partial agonists at the 5 - HT_{1A} receptor. They are antagonistic at 5 - HT_6 (or) 5 - HT_7 receptor [29].

Of these drugs , Risperidone is similar to high potency first generation antipsychotics . It acts by blocking D_2 receptors in the mesolimbic area and so the positive symptoms are improved . It blocks $5HT_2$ receptors in the cortex and so the negative symptoms are improved. It is antagonistic at D_1 , D_4, histamine , Ach and α_1 receptors[34].

FIG 2

STRUCTURE OF RISPERIDONE



DEPOT PREPARATIONS :

Depot preparations have been developed which have long duration of action, convenient and increase patient compliance . The preparations available are :

- ✓ **Fluphenazine decanoate** administered every 2 - 4 weeks
- ✓ **Haloperidol decanoate** administered every 2 - 4 weeks
- ✓ **Risperidone** in the form of carbohydrate microspheres administered every 2 - 3 weeks
- ✓ **Flupenthixol decanoate** administered every 2 - 4 weeks

- ✓ **Zuclopenthixol acetate or decanoate** administered every 1 - 4 weeks[35].

PHARMACOKINETICS :

Most of the antipsychotic drugs are incompletely absorbed. They undergo significant first pass metabolism. They are lipid soluble. They are 92 - 99 % protein bound. They have large volumes of distribution. They generally have a longer duration of action. Most antipsychotics are completely metabolised by oxidation (or) demethylation[29].

ADVERSE EFFECTS :

ADVERSE EFFECTS RELATED TO MONOAMINE RECEPTORS:

Dopamine D_2 receptor :

All antipsychotic agents possess D_2 antagonist properties with the exception of the D_2 partial agonist, Aripiprazole. The strength of this antagonism determines the likelihood for EPS, akathisia, hyperprolactinemia and long term tardive dyskinesia risk.

TABLE 3 : NEUROLOGICAL SIDE EFFECTS OF ANTIPSYCHOTIC DRUGS

REACTION	FEATURES	TIME OF ONSET & RISK INFO	PROPOSED MECHANISM	TREATMENT
Acute Dystonia	Spasm of muscles of face , tongue , neck & back .	Time : 1 - 5 days Young , Antipsychotic Naive patients at high risk	Dopamine Antagonism	Diphenhydramine 25-50 mg IM , or benztropine 1-2 mg IM .
Akathisia	Subjective and objective restlessness; not anxiety or "agitation"	Time: 5-60 days	Unknown	Reduce dose or change drug ;Clonazepam, Propranolol more effective than anti - parkinsonian drugs .

Parkinsonism	Bradykinesia, Rigidity ,Variable tremor,mask facies, Shuffling gait	Time : 5 - 30 days . Elderly at great risk	DA antagonism	Dose reduction ; Change medication : Amantadine
Neuroleptic Malignant Syndrome	Extreme rigidity , fever, Unstable BP, Myoglobinemia ; It can be fatal .	Time : weeks to months . Can persist for days after stopping antipsychotic	Dopamine antagonism	Stop antipsychotic immediately ; Supportive care : Dantrolene & Bromocriptine
Perioral tremor ("Rabbit syndrome ")	Perioral tremor (may be a late variant of parkinsonism)	Time : Months or years of treatment	Unknown	Amantadine

Tardive dyskinesia	Orofacial dyskinesia	Time : Months or years of treatment . Elderly at 5 fold risk .	Postsynaptic DA receptor supersensitivity , upregulation	May be reversible with early recognition &drug discontinuation .

H_1 receptors :

Central antagonism of H_1 receptors is associated with two major adverse effects : Sedation and weight gain via appetite stimulation . Appetite stimulation is the primary mechanism involved , with little evidence to suggest that decreased activity (due to sedation) is a main contributor of antipsychotic - related weight gain [36] .

The low potency Phenothiazine, Chlorpromazine and atypical antipsychotic drugs Olanzapine and Clozapine are the agents of highest risk with mean annual weight gain of 13 kgs . High-potency typical antipsychotic drugs (e.g., haloperidol, fluphenazine) , and newer atypical antipsychotics Asenapine , Ziprasidone , and Aripiprazole are associated with mean annual weight gains < 2 kg in schizophrenia patients with mean gains of 2.5-3 kg noted for iloperidone , risperidone, and quetiapine [37] .

M_1 receptors :

- Clozapine , Low potency Phenothiazines - Significant anti - cholinergic activity .
- Risperidone , Paliperidone , Asenapine , Iloperidone , Ziprasidone , Aripiprazole - No appreciable anti - cholinergic effect .
- Quetiapine - modest muscarinic affinity but its active metabolite , Norquetiapine is likely responsible for anti - cholinergic complaints [38] .

α_1 receptors :

- Risk of orthostatic hypotension .
- Low potency typical agents - Greater risk for orthostasis .

ADVERSE EFFECTS NOT RELATED TO MONOAMINE RECEPTORS :

Adverse metabolic effects :

- Atypical antipsychotics are associated with glucose dysregulation .
- Certain atypical antipsychotics and low potency conventional agents have been associated with hyperlipidemia .

Adverse cardiac effects :

- Thioridazine, Mesoridazine, Pimozide, i.m Droperidol & i.v Haloperidol are reported to cause Torsades de pointes and subsequent ventricular arrythmias due to inhibition of cardiac K^+ channels .

Other adverse effects :

- Seizure risk - more common with Carbamazepine and Clozapine .
- Clozapine induced agranulocytosis is immune mediated and those patients should not be rechallenged .
- Thioridazine causes pigmentary retinopathy at daily doses > 800 mg / day .
- Low - potency phenothiazines are associated with the development of photosensitivity [3] .

CHOICE OF ANTIPSYCHOTICS :

Since the early 1990's , Second generation antipsychotics have been used widely with the belief that these agents were more effective, better tolerated and ultimately more cost - effective than first generation antipsychotics . Only limited studies comparing first and second generation existed . To address this knowledge gap , the National Institute of Mental Health (NIMH) sponsored the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study [39] .

CATIE study was designed to compare the effectiveness of four second generation antipsychotics (Olanzapine , Quetiapine , Risperidone , Ziprasidone) and a representative first generation antipsychotic (Perphenazine) in " real world " Schizophrenia patients . Phase II CATIE study suggested that Olanzapine and Quetiapine were more effective

than Risperidone , in patients who failed to respond to Perphenazine [40] . However , the CATIE cost - effectiveness analysis found Perphenazine to be less costly and similarly effective than each of the atypical antipsychotics [41] .

Similarly to the NIMH - sponsored CATIE study , the United Kingdom's National Health Service funded the Cost Utility of the Latest Antipsychotic drugs in Schizophrenia study (CUtLASS) This study found no difference between first and second generation antipsychotics in terms of quality of life .

- Clozapine should be considered for patients who have failed to respond to other second generation medications .
- Long Acting Injectables (LAI) may be considered for patients with poor adherence .
- First generation agents clearly have the highest risk of EPS and tardive dyskinesia [42] .
- Risperidone and the newly available Paliperidone tend to increase serum prolactin levels and tend to cause EPS at higher doses .
- Although weight gain and metabolic disturbances are associated with all of the second generation agents (with the possible exception of Ziprasidone and Aripiprazole) . Olanzapine and Clozapine appear to have the highest likelihood of causing these side effects [43] .

- Sedation is commonly observed in patients receiving Quetiapine , Olanzapine and Clozapine .
- Both Ziprasidone and Paliperidone carry product labeling for QT_c prolongation and should be used cautiously in patients at risk for QT_c prolongation [1] .
- Risperidone and Aripiprazole is FDA approved for irritability associated with autism in child and adolescent patients aged 5 - 16 years .
- Antipsychotics carry pregnancy class B (or) class C warnings .
- Medications with significant anti cholinergic property should be particularly avoided in elderly patients .
- α_1 antagonists also should be avoided in elderly patients with poor vasomotor tone [3] .
- Finally , Clozapine , because of its side effects of granulocytosis , seizures and myocarditis is generally reserved for patients with treatment resistant illness or suicidality [1] .

MANAGEMENT OF VARIOUS CONDITIONS :

ACUTE PSYCHOSIS :

Acute phase is characterized by psychotic symptoms and often by agitation and lasts from 4 to 8 weeks [6] . This phase is managed with the use of high potency first generation antipsychotics either

alone (or) in conjunction with a Benzodiazepine (such as Lorazepam) and / (or) an anticholinergic drug (such as Benztropine).

FIRST EPISODE PSYCHOSIS :

Because of the most favourable neurological side - effect profile mainly the reduced risks of adverse neurological events , second generation antipsychotics are often considered for the initial treatment of first episode psychosis [1].

MAINTENANCE TREATMENT :

The major goals of maintenance treatment are prevention of relapse and improvement in psychosocial and vocational function . Several studies have demonstrated that higher rates of relapse are associated with medication discontinuation [44,45,46] . Even after recovery from acute symptoms, this phase of treatment lasts for 6 months [6] .

All available atypical antipsychotics have been granted U. S FDA approval for the maintenance treatment of Schizophrenia . Moreover , some evidence suggests that atypical antipsychotics may be more effective than conventional agents in forestalling relapse [47,48] .

TREATMENT - RESISTANT SCHIZOPHRENIA :

For research purposes , Kane et al operationally defined treatment resistance as

1) Lack of significant response to atleast three adequate trials of neuroleptics from atleast two different chemical classes in the past five years .
2) Persistently poor social and occupational functioning [49,50,51] . Most of the available data suggest that Clozapine is the most effective drug for treatment resistant Schizophrenia [1] .

II . PHYSICAL METHODS :

1) Electroconvulsive therapy (ECT) :

ECT is a biological therapy , wherein seizures are induced under medical supervision by passing electric current across the scalp . ECT helps to control the excitement , violence & aggression in acute Schizophrenia in usually 3 sittings . A combination of ECT and neuroleptics have better effects than ECT alone(or) neuroleptics alone [52].

2) Psychosurgery :

Psychosurgery is defined as a surgical intervention to disconnect fibres connecting one part of brain with another with the intent of modifying the behavior , thought (or) mood disturbances for which there is no organic pathology [23] .

It is not considered an appropriate treatment nowadays . It is practiced only for severe , intractable cases [53].

III . PSYCHOSOCIAL INTERVENTIONS :

Psychosocial therapies are intended to increase the social abilities, interpersonal communication , self - sufficiency and practical skills in patients with Schizophrenia .

A) Social skills training :

Also referred to as behavioral skills therapy . Videotapes , role playing , homework assignments for the specific skills are currently used in therapy.

B) Family oriented therapies :

The aim of this therapy is to identify and avoid the potentially troublesome situation in family and if it emerges , resolve the problem quickly .

C) Cognitive behavioral therapy :

CBT has been devised to improve cognitive distortions , decrease the distractability and correct the errors in judgements among schizophrenia patients .

D) Vocational therapy :

Various methods are used to help patients regain their old skills (or) develop new ones . These include job clubs , sheltered workshops and transitional employment programs [20] .

EMERGING TARGETS AND THERAPEUTICS IN SCHIZOPHRENIA :

Several new molecular targets are being actively pursued. They are as follows .

a) NMDA agonists :

- ✓ Agents like glycine [54] , serine [55] and D - Cycloserine [56] bind to the allosteric facilitator glycine binding site to increase efficiency at the NMDA receptor .
- ✓ mGlu 2 / 3 receptor agonist LY2140023 proved effective in phase II Schizophrenia trial [57] .
- ✓ Glycine is a co - transmitter at glutamate receptors. Gly T_1 inhibitor SSR 504734 was effective in blocking PCP - induced CNS metabolic changes in rats [3] .

b) Muscarinic agents :

- ✓ M_1 and M_2 muscarinic receptor modulators have passed several preclinical antipsychotic tests [58] .
- ✓ M_1 / M_4 agonist Xanomeline has precognitive and antipsychotic affects in Schizophrenia trials [59] .

c) Nicotinic agents :

Agonists at α_7 [(60)] and $\alpha_4\beta_2$ [(61)] nicotinic receptors are under trial as Schizophrenics have deficits in nicotinic Ach receptor function .

d) Phosphodiesterase (PDE) inhibitors :

PDE inhibitors that degrade cAMP has met the criteria for antipsychotic agents in preclinical studies [62,63] .

e) Erb B antagonists :

As Neuregulin (NRG) and its receptor erb B are implicated in the pathophysiology of Schizophrenia , erb B antagonists are tried as a novel approach in the treatment of Schizophrenia [64,65,66].

f) Others :

Lurasidone is a novel 5HT / DA antagonist under trial [3] .

METABOLIC SYNDROME:

Metabolic syndrome (Met S) is a complex disorder considered a worldwide Epidemic [67]. Although Hims worth reported insulin resistance in diabetes in 1939[68], insulin resistance syndrome as a separate entity was reported in 1988 by Reaven . It included hyperglycemia , insulin resistance , hypertension , high VLDL triglycerides and low HDL cholesterol and was also called as syndrome - X [69]. Surprisingly he missed visceral obesity from the definition and later added it as a crucial abnormality[70] .

Since then, many international organizations and expert groups , such as the World Health Organization (WHO), the European Group for the study of Insulin Resistance (EGIR) , the National Cholesterol Education Program Adult Treatment Panel III (NCEP : ATPIII) , the American Association of Clinical Endocrinology (AACE) , the International Diabetes Federation (IDF), and the American Heart Association / National Heart , Lung , and Blood Institute (AHA/NHLBI) , have attempted to incorporate all the different parameters used to define Met S [67] . The first attempt was made in 1998 by the WHO , which proposed the following criteria for metabolic syndrome .

WHO CLINICAL CRITERIA FOR METABOLIC SYNDROME .

Insulin resistance , identified by one of the following:

- ✓ Impaired fasting glucose
- ✓ Type 2 diabetes
- ✓ Impaired glucose tolerance

Plus any two of the following:

- ✓ Plasma triglycerides ≥ 1.7 mmol/L
- ✓ Antihypertensive medication and / or high blood pressure (≥140 mm Hg systolic or ≥ 90 mm Hg diastolic)
- ✓ BMI > 30 kg / m^2 and / or waist : hip ratio > 0.9 in men , > 0.85 in women
- ✓ Urinary albumin excretion rate ≥ 20 μg / min or albumin : creatinine
- ✓ ratio ≥ 3.4 mg / mmol [71]
- ✓ HDL cholesterol < 0.9 mmol / L in men or < 1.0 mmol / L in women

Some studies have suggested increased levels of inflammatory markers such as, C reactive protein (CRP) as an important predictor of cardiovascular risk in patients with metabolic syndrome[72]. Among the drugs , HAART therapy and atypical antipsychotics carry high risk for metabolic syndrome .

The metabolic syndrome appears to affect around 10 to 25 percent of adult population worldwide[73] . In India , both insulin resistance and the metabolic Syndrome has wide prevalence[74]. The Jaipur Heart Watch Studies have reported the prevalence of metabolic syndrome among urban Indians as 18.4% in men and 30.9% in women and 24.9% overall[75]. The age - related prevalence seems to be escalating in both men and women[70] .

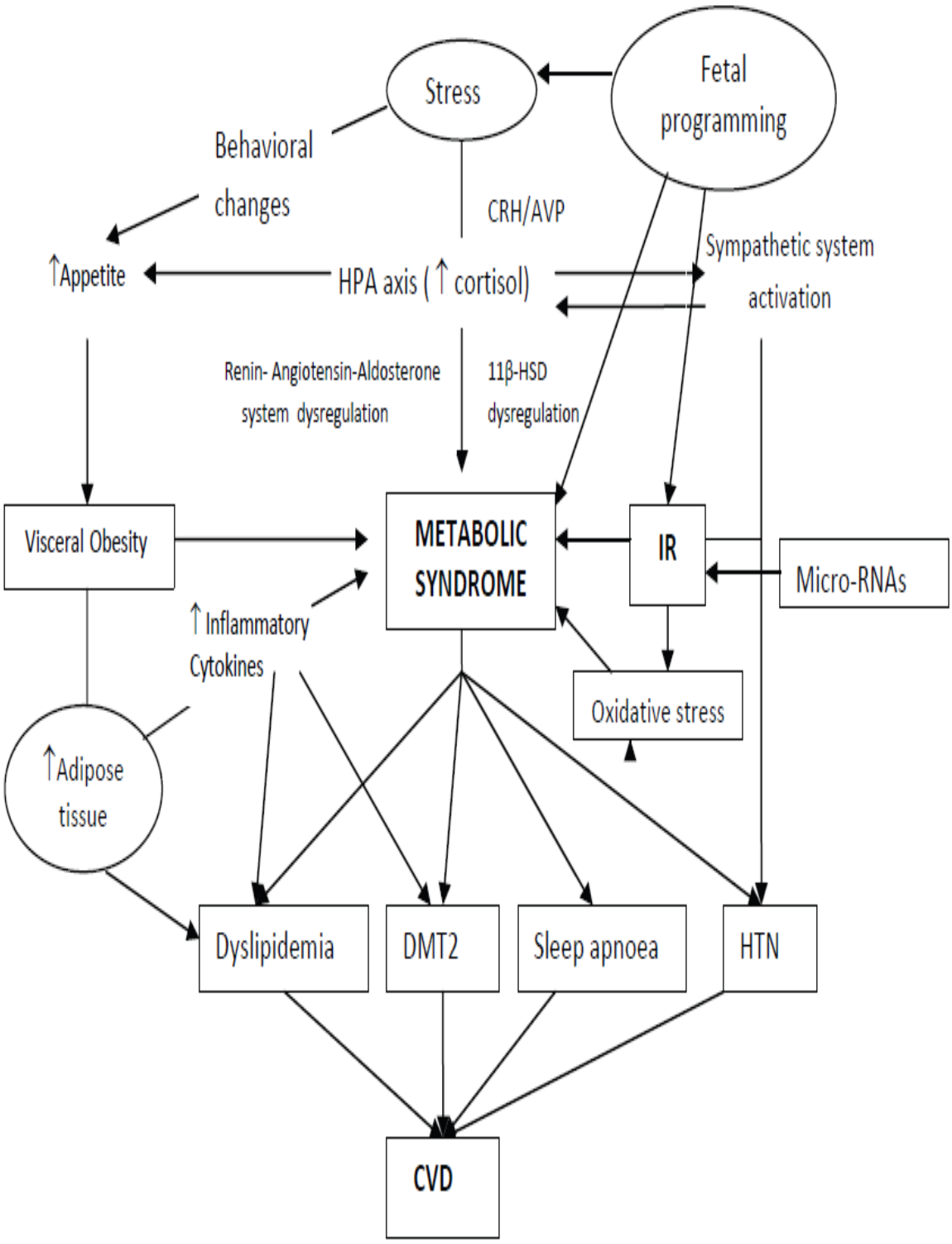


Figure 3: Schematic image of the conditions implicated in the patho physiology of Metabolic syndrome and the potential interactions[67]

METABOLIC SYNDROME AND ATYPICAL ANTIPSYCHOTICS

Possible mechanisms:

1) **Weight regulation** is a complex balance of energy intake , storage and expenditure driven by both endocrine mechanisms and central nervous system .

a) CNS system drives :

- ✓ Satiety - Desire to limit further food intake after completing a satisfying meal .
- ✓ Appetite - Desire for food (or) drink
- ✓ Craving - An intense desire (or) longing .

b) Endocrine actions :

- ✓ Energy utilisation
- ✓ Metabolism

c) Imbalance between energy ingestion and energy expenditure leads to weight gain .

II) Receptor mediation of neurotransmitters and hormones :

a) 5 HT_{2c} receptor :

- ✓ Decreased food consumption occurs either due to increased serotonin concentrations in the synaptic cleft (or) due to direct activation of $5HT_{2c}$ receptor .
- ✓ Antagonistic effect at 5 HT_{2c} receptor induces opposite effect .

b) Histamine - 1 receptor :

- ✓ Regulates arousal and appetite .
- ✓ H_1 receptor antagonism causes increase in appetite and weight gain .
- ✓ Binding studies reveal that sedation and weight gain are directly proportional to the ability of the agent to block H_1 receptors .

TABLE 4

RELATIVE RECEPTOR BINDING AFFINITIES OF ATYPICAL ANTIPSYCHOTICS [80]

Receptor	Risperidone	Olanzapine	Quetiapine	Clozapine
H_1 Histaminergic	++	++++	++++	++++

c) Leptin :

- ✓ Leptin is a member of IL - 6 family .
- ✓ It is secreted by white adipose cells .
- ✓ Insulin secretion is regulated by leptin .
- ✓ Energy metabolism in skeletal muscle and fat cells is regulated by leptin.
- ✓ Leptin resistance is the obesity associated with malfunctioning lepin receptors.

d) Poor self care

e) Sedentary lifestyle

f) Unhealthy dietary habits [76,77,78,79]

Morbidity and mortality :

- ✓ The prevalence of metabolic syndrome in adults with schizophrenia varies between 20 % and 60 % .This is actually twice that of the normal healthy population [81] .
- ✓ The prevalence of metabolic syndrome in patients without glucose abnormalities was 17.5 % (ATP - III criteria) and 21.5 % (IDF) [82].
- ✓ Also, it has been found that the prevalence of dyslipidemia, hypertension , obesity and type II diabetes mellitus is around 1.5 to 2 times greater in individuals with schizophrenia compared with the general population [83] .
- ✓ Cardiovascular mortality accounts for a total of 34 % of deaths among the male patients and 31 % of deaths among the female patients with schizophrenia [84,85] .

MONITORING PROTOCOL :

Appropriate baseline screening and ongoing monitoring are essential in patients taking atypical antipsychotic drugs .

Baseline monitoring

The baseline screening should be done before or soon after the initiation of any antipsychotic medication . These include

- ✓ Personal and family history of obesity , diabetes , dyslipidemia , hypertension , or cardiovascular disease
- ✓ Waist circumference (at the level of the umbilicus)
- ✓ Weight and height (so that BMI can be calculated)
- ✓ Fasting lipid profile
- ✓ Blood pressure
- ✓ Fasting plasma glucose

Follow up monitoring :

- ✓ Weight must be reassessed at 4 , 8 , and 12 weeks of initiating the SGA therapy and thereafter every 3 months at the time of routine visits .
- ✓ Waist circumference to be assessed annually .
- ✓ Blood pressure and fasting blood glucose levels should be assessed at 12 weeks and after one year of initiation of therapy and fasting lipid profile at 12 weeks and 5 yrs [76] .

MANAGEMENT OF METABOLIC SYNDROME :

I. Pharmacological strategies

II. Non - pharmacological interventions .

I . Pharmacological strategies :

A. Switching the medication

B. Medication to effect weight loss or prevent weight gain

A) Switching the medication :

Switching from an antipsychotic medication to another has significant effect on metabolic parameters and body weight . Results of CATIE trials suggest that switching to an antipsychotic drug with a neutral metabolic profile provide a beneficial weight change .There was a significant reduction in body weight, waist circumference and blood pressure when Risperidone was substituted for Olanzapine [86] .

B) Medication to effect weight loss or prevent weight gain :

Many controlled clinical trials have shown that obesity drugs in combination with lifestyle therapy provide modest efficacy [87] . Phenyl propanolamine [88] and D - Fenfluramine [89] are removed from the market because of adverse effects . Rimonabant is an anorectic anti - obesity drug that has been withdrawn from the market due to serious adverse effects .

a) Nizatidine :

Nizatidine is a histamine H_2 receptor antagonist . Nizatidine (150 mg twice daily) was tried for Olanzapine - induced weight gain . Nizatidine showed weight loss compared to placebo. Nizatidine was well tolerated. No patients dropped out of the study but the interpretation was limited by the short study duration and small sample size [90].

b) Famotidine :

Famotidine is another H_2 antagonist . A study was done to assess the effect of Famotidine in preventing the Olanzapine - induced weight gain in schizophrenia patients . Famotidine was not effective in reducing the weight gain . Results gave the inference that H_2 antagonists have only limited utility in weight control [91].

c) Fluoxetine :

Fluoxetine is an antidepressant with selective serotonin reuptake inhibiting property . A study was conducted using higher doses of Fluoxetine (60 mg daily) for treating patients who gained more than 3% of their weight with Olanzapine . The conclusion of the study was that the Fluoxetine did not have any weight reducing effect [92].

d) Reboxetine :

Reboxetine is a selective norepinephrine reuptake inhibitor . Weight gain with Reboxetine was lesser in the treatment group . Reboxetine was well tolerated . However the study was weakened by its short duration [93].

e) Amantadine :

Amantadine is an antiparkinsonian drug . Amantadine showed a greater weight loss at Weeks 8 , 12 , and 16 compared with placebo when added to individuals who had experienced weight gain of 5% or more with Olanzapine [94] . Amantadine was well tolerated .

f) Sibutramine :

Sibutramine has the property of inhibiting the reuptake of serotonin and nor epinephrine . Hence it is approved for long - term treatment of obesity. Sibutramine caused more weight loss when compared to placebo group in a trial . There was also a mean (SD) increase in blood pressure of 2.1 (8.5) mm Hg and a relative decrease of Hb A_{1C} in the sibutramine group. Sibutramine reported no worsening of psychotic symptoms [95].

g) Topiramate :

Topiramate is an anticonvulsant medication that has been used also for bipolar affective disorder and for losing weight . Topiramate 200 mg and not Topiramate 100 mg was effective in inducing weight loss in a study conducted in Korea .The frequent side effect with Topiramate was Paresthesia . Serious side effects such as metabolic acidosis were not reported . There was no worsening of cognitive impairment or psychotic symptoms [96].

h) Orlistat :

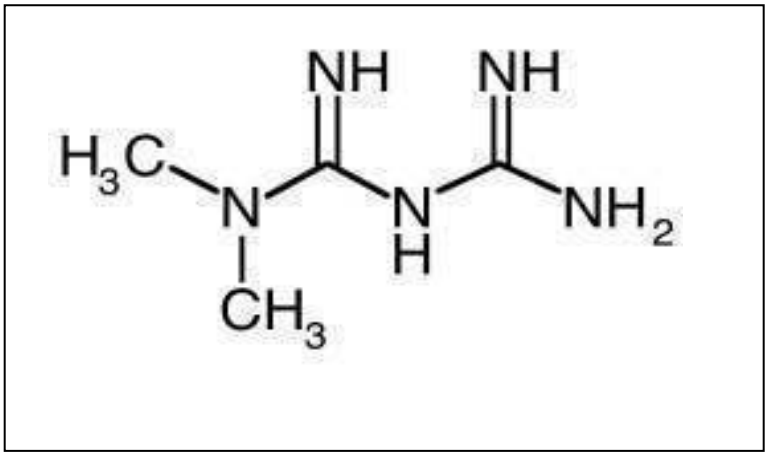
Orlistat , a lipase inhibitor caused greater changes in waist circumference , body mass index (BMI) and insulin resistance compared to the controls [97].

h) Metformin :

Only Metformin in the biguanide class of oral hypoglycemic drugs is available for use today [98] .

FIGURE4

STRUCTURE OF METFORMIN



Mechanism of action :

- ✓ Metformin increases AMPK activity (AMP - dependent protein kinase)[99].
- ✓ When cellular energy stores are reduced , AMPK is activated by phosphorylation .
- ✓ Activated AMPK stimulates glucose uptake , fatty acid oxidation and non oxidative metabolism .
- ✓ Activated AMPK reduces gluconeogenesis and lipogenesis .

- ✓ The net result of these actions is lower rates of hepatic glucose production , lower blood glucose levels , increased glycogen storage in skeletal muscle and increased insulin sensitivity [10] .

Pharmacokinetics :

Metformin is absorbed primarily from the small intestine . Its transport into cells is mediated in part by organic cation transporters [10]. Half - life of Metformin is 1.5 – 3 hours. Metformin is not plasma protein bound. It is not metabolized and hence excreted unchanged by the kidneys [29] .

Adverse effects :

- ✓ The most common adverse effects of Metformin are gastrointestinal (anorexia, nausea, vomiting, abdominal discomfort, and diarrhea), Which occur in up to 20 % of patients .
- ✓ Lactic acidosis is less common with Metformin [29] .
- ✓ Metformin use is associated with 20 - 30% lower blood levels of vitamin B_{12} [100].

II . Non - pharmacological interventions :

The key components for the non pharmacologic management obesity are diet[81] , exercise[102] and behavioral therapy[103] .

NOVEL APPROACHES :

1) Ramipril :

Ramipril is an ACE inhibitor . It has been found to reduce the cardiovascular morbidity and mortality by preserving endothelial function and slowing the progression of atherosclerotic plaque formation. It thereby reduces plaque activation and prevents the development of type 2 diabetes probably by reducing insulin resistance. Hence, Ramipril may be tried as a first choice antihypertensive agent in an individual with hypertension associated with metabolic syndrome [104] .

2) Acarbose :

Acarbose is an inhibitor of α - glucosidase . Reduction in risk of developing cardiovascular events and reversion to normal glucose tolerance was significantly greater with Acarbose [105].

3) PPAR-γ agonists :

Pioglitazone reduces multiple components of metabolic syndrome such as hypertension , high FBS and triglycerides . This drug also causes decrease in urinary albumin / creatinine ratio [106] .

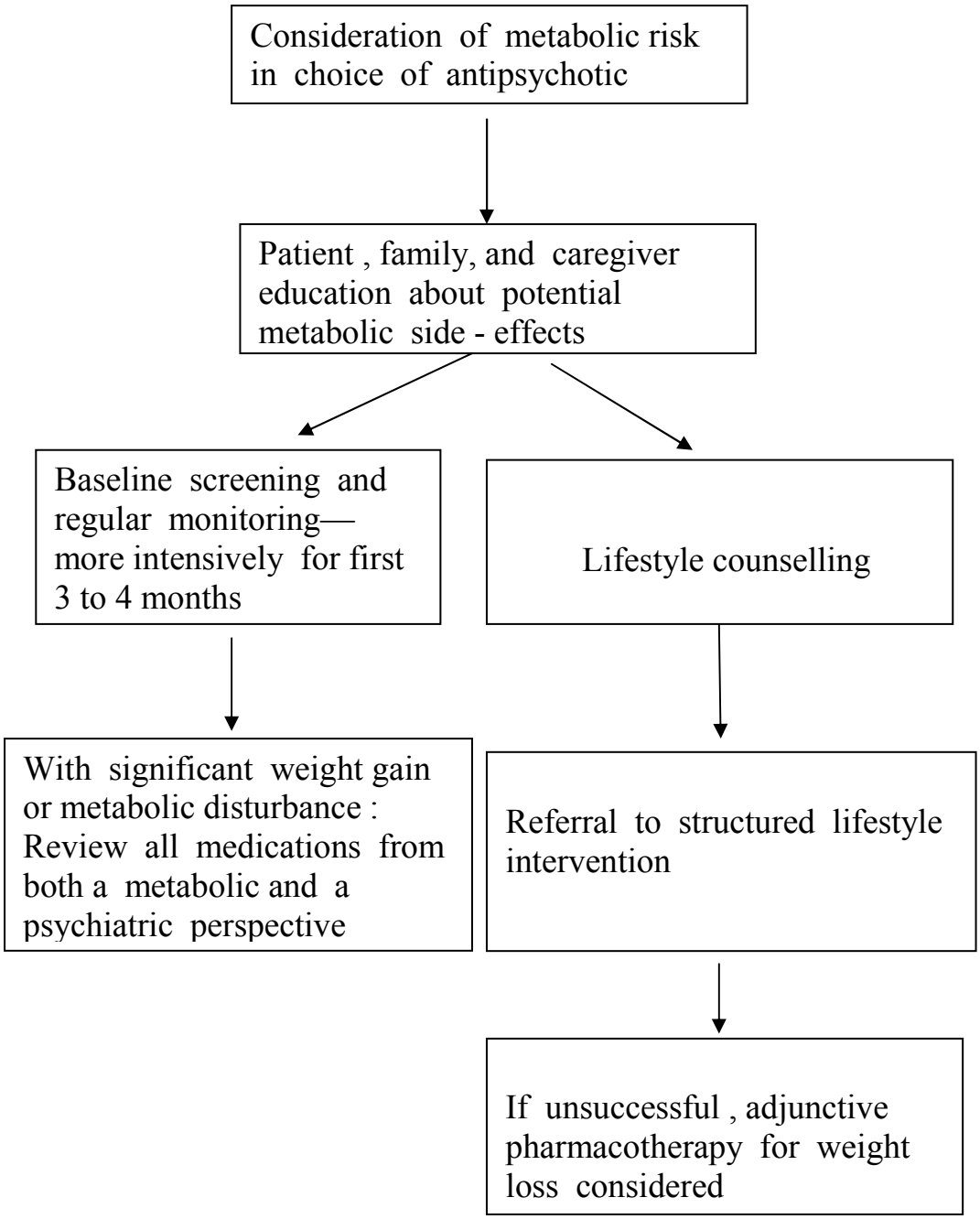
4) Omega-3 fatty acids :

In metabolic syndrome patients, 3 gm of fish oils (Omega-3 fatty acids) have been found to decrease ApoB production, decrease triglycerides by 20% and marked reduction in small dense LDL [107].

5) Surgical management :

The exact mechanism of surgical procedures for obesity remains unknown . A Meta - analysis involving 136 studies showed that type II diabetes got improved in 86.0% of patients who had undergone bariatric surgery. In many developed countries , bariatric surgery has been used for severe obesity [108]. Long - term results are not available . Safety issues are in doubt due to the recent reports of mortality and morbidity of the procedure in the elderly [109] .

TREATMENT ALGORITHM FOR THE MANAGEMENT OF METABOLIC DISTURBANCES IN PATIENTS TREATED WITH ANTIPSYCHOTIC MEDICATIONS [110]



CLINICAL STUDIES ON RISPERIDONE :

1. A meta analytical study was conducted by Allison et al who collected 81 non - english and english articles that included the data on weight change in antipsychotic treated patients . The results gave the inference that among the newer antipsychotic agents , mean increase in weight with Risperidone was 2.1 kg[111] .
2. In a 3 month study done on 56,849 patients with schizophrenia , Leslie et al concluded that the diabetic risk for Risperidone was the least with the hazard ratio of 1.01 and the attributable risk of diabetes mellitus associated with Risperidone was 0.05 %[112] .
3. According to a study conducted in USA among 147 patients taking Risperidone for 3 months with a mean age of 40.9 , Meyer et al suggested that the incidence of metabolic syndrome was 30.6% based on ATP - III A criteria[113] .
4. An Indian study done by Gautam et al revealed that among 90 patients given II generation antipsychotics , 10 % of patients taking Risperidone developed metabolic syndrome after 4 months of medication[114] .
5. With the mean dose of 3.6 mg/day of Risperidone for 12 weeks in first episode psychosis patients , Iglesias et al found that the significant weight gain with Risperidone was 5.6 kg (S.D = 4.5).

However there were no significant changes in glucose metabolism after 12 weeks[115] .

CLINICAL STUDIES ON METFORMIN:

1. In a historical cohort study by Mourao Junior et al involving 57 type 2 diabetes patients with metabolic syndrome and on insulin who were assessed by a paired analysis before and after the addition of Metformin , it was found that there was significant reduction ($p<0.05$) of BMI (30.7 ± 5.4 to 29.0 ± 4 kg/m^2) and WC (124.6 ± 11.7 to 117.3 ± 9.3 cm) with Metformin[116] .
2. Yanovski et al conducted a randomized , double blind , placebo controlled trial consisting of 100 severely obese , insulin resistant children aged 6 - 12 years randomized to 1000 mg Metformin (or) placebo for 6 months followed by a open - labelled Metformin treatment for 6 months and concluded that Metformin had significantly caused greater decrease in BMI (difference , -1.09 kg/m^2, $p=0.006$) . Fasting glucose ($p=0.007$) improved more in Metformin treated children than in placebo treated children[117] .
3. Wulffele et al reviewed 41 studies that included that included randomized controlled trial in patients with type II diabetes mellitus and Metformin treatment lasting for atleast 6 weeks and demonstrated that there was significant reduction in plasma triglycerides [diff (-0.26) (-0.34 to -0.18) mmolL^{-1} , $p<0.0001$] [118].

4. Double - blind , placebo controlled study involving 29 adolescents was conducted by Freemark et al and it revealed that Metformin caused a progressive decline in FBS (from a mean of 84.9 to 75.1 mg%) and a decline of 0.12 standard deviation in study participants (-1.3% from baseline)[119] .

CLINICAL STUDIES ON METFORMIN ALONG WITH ATYPICAL ANTIPSYCHOTICS:

1. Wu et al conducted a randomized control trial involving 40 first episode psychosis patients to determine the impact of Metformin in patients newly commenced on Olanzapine . Patients had a mean age of 25 years and normal BMI at study beginning . Weight , BMI , waist to hip ratio levels ,WC increased less in the Olanzapine + Metformin group relative to Olanzapine + Placebo group during 12 week follow up period[8] .
2. Study conducted by Baptista et al in 40 patients with schizophrenia with a mean age of 47.7 years , investigated the efficacy of Metformin in patients newly commenced on Olanzapine . This is the only study investigating Metformin for prevention of weight gain in chronic patients newly commenced on II generation antipsychotic medications . This RCT showed reduction in blood sugar levels and triglycerides independent of weight loss in the Metformin group[120] .

With the above extensive literature review , due to the feasibility of Risperidone and Metformin in our hospital setting and due to the paucity of trials using both these drugs , we conducted this study using Metformin and Risperidone to evaluate the effectiveness and safety of Metformin along with Risperidone to prevent antipsychotic - induced metabolic syndrome in first episode schizophrenia patients.

AIM OF THE STUDY

To evaluate the effectiveness and safety of Metformin along with Risperidone to prevent antipsychotic - induced metabolic syndrome in first episode schizophrenia patients.

METHODOLOGY

STUDY DESIGN :

Open - labelled, randomized, prospective, comparative, single centered, parallel group study .

STUDY DURATION :

March 2013 - February 2014 .

STUDY CENTRE :

Department of Psychiatry , Tirunelveli Medical College Hospital , Tirunelveli .

SAMPLE SIZE :

Total of 96 patients (48 each in group).

INCLUSION CRITERIA:

- Patients with 18 to 40 years of age who have been diagnosed with first episode schizophrenia based on DSM - IV criteria and on treatment with T . Risperidone 2 mg twice a day for ≤ 2 months .

EXCLUSION CRITERIA:

- Uncooperative , aggressive patients .
- Patients with suicidal tendency .
- Pregnant and lactating women.

- Patients with history of liver disease/ renal disease/ cardiovascular disease/ diabetes mellitus/ hypertension/ dyslipidemia/ substance abuse / seizure disorder / malignancy .
- Patients with diagnosis other than schizophrenia .
- Patients with mental retardation .
- Patients who are taking other drugs that may affect body weight (Carbamazepine, Lithium, Topiramate, antidepressants, Valproate and hormone replacement therapy)
- Patient who is on special diet or who do exercise for weight loss.

ETHICAL CONSIDERATIONS :

The study was commenced after getting approval from the Institutional Ethical Committee . Written informed consent was obtained in local vernacular language from every patient (or) his reliable caregiver before enrollment .

SCREENING :

Based on the inclusion and exclusion criteria, the subjects were enrolled in the study after initial screening . Initial screening at baseline included clinical assessment, anthropometric measurements like weight, height and waist circumference and laboratory investigations like complete blood count, fasting blood sugar, serum urea , serum creatinine, liver function tests , routine urine analysis and fasting lipid profile .

RANDOMISATION AND ENROLLMENT :

Subjects who were initiated on T . Risperidone 2 mg orally twice daily for ≤ 2 months for first episode schizophrenia were randomized using computer generated table into two groups .

GROUP 1 : Patients were given T. Risperidone 2 mg alone , orally , twice daily after food .

GROUP 2 : Patients were given T.Metformin 500 mg orally , twice daily after food along with T.Risperidone .

T.Risperidone and T.Metformin remained at a fixed dose as baseline levels throughout the course of treatment . All subjects were under the care of another adult caregiver (or) their parents who monitored and recorded drug intake everyday to confirm adherence .

CONCOMITANT MEDICATIONS :

Only T. Trihexyphenidyl (5 - 10 mg/day) for extrapyramidal symptoms (or) T.Lorazepam (1-3 mg/day) for insomnia (or) agitation were given when needed .

COMPLIANCE :

The compliance in both the group of patients were assessed using pill count . Patients were asked to return the empty strips when they come for receiving the drugs .

EFFICACY PARAMETERS :

PRIMARY ENDPOINT :

A. Proportion of patients developing metabolic syndrome at the end of 6 months in both the groups .

SECONDARY ENDPOINTS :

B. Changes in body mass index from baseline to the end point (after 6 months of treatment) .

C. Proportion of patients progressing a stage higher from the baseline in terms of BMI at the end of 3 months .

D. Changes in waist circumference from baseline to the end point .

E. Changes in fasting blood sugar from baseline to the endpoint .

F. Changes in fasting triglycerides from baseline to the endpoint .

All the above parameters were assessed in fasting state . Fasting as confirmed with patients (or) caregivers at the time of assessment.

Parameter assessment :

A) Body Mass Index (BMI) measurement :

Height :

All subjects were instructed to remove their shoes and socks before the procedure . Subjects were instructed to stand on a level floor with the feet parallel and pointing forwards . Subjects were asked to stand unsupported by not touching the nearby wall (or) furniture . Subjects were asked to stand as tall as possible such that the the

lower border of the left orbit and the upper margin of the external auditory meatus remain horizontal. Subjects were instructed to breathe out gently during the measurement. The measure was placed on the subjects head to ensure that the spirit level is balanced. The measured height was expressed in centimeters.

Weight :

The subjects were instructed to remove the shoes, excess clothing and overcoats . Pockets containing keys and wallet was emptied . Any heavy jewellery worn by the subject was removed. Weight was measured using a manual weighing scale . The weighing scale platform was placed on an even floor surface . Before the subject stepped onto the platform , it was ensured that the viewfinder displayed [0.0] before the measurement. The subjects were instructed to stand still on the scales platform. Subjects were asked to stand free without leaning on a chair (or) wall. Subjects were instructed to exhale gently during the measurement. The weight was measured in kilograms . Once the weight was recorded , the subjects were instructed to stand off the platform and re-apply their over clothes and shoes .

BMI calculation :

BMI (or) Quetelet index was calculated using the formula [weight(kg) / (height (m))^2] . BMI was graded as follows .

Underweight - < 18.5

Normal - 18.5 to 25

Overweight - 25 to 30

Obese - > 30 .

Also the proportion of subjects progressing from a stage at baseline to the next higher stage at 3 months were noted in both the groups and entered in a 2 × 2 table .

B) Waist circumference :

The subjects were instructed about the procedure and permission acquired to remove the clothing as it may restrict the accurate measurement. A flexible measuring tape was used to measure the waist circumference in standing position. It was ensured that the tape was neither tight nor loose such that it fits snugly. Subjects were instructed to breathe out normally during the measurement and the waist circumference was measured at a point midway between the lowest rib and greater trochanter with the subject's hands placed loosely by the side. Waist circumference was rounded off to nearby whole number and expressed in centimeters .

C) Blood investigations :

Patients were previously instructed to come for follow up visits with 10 hrs of fasting. The subjects were made to sit comfortably in a chair and informed about the procedure. After sterilizing our hands

upto the elbows , a tourniquet was placed 3 to 4 inches above the selected puncture site neither tight nor too loose in the subjects not longer than 1 minute. Then after wearing the non - latex glove , the vein was palpated and the area above it was cleansed and air dried. The subject was asked to make a fist and the arm was firmly grasped to make the skin taut and vein anchored such that at an angle of 15 - 30 degrees with the arm surface , needle was inserted and 2 ml of blood was withdrawn. Blood was collected in a sterilized, dry container for further investigation .

✓ **Fasting blood sugar** :

Using the sample as obtained above, fasting blood sugar levels were assessed using the auto analyzer.

✓ **Fasting Triglycerides :**

Using the sample as obtained above, fasting triglyceride levels were assessed using the auto analyzer.

FOLLOW UP VISITS :

Follow up was done at the end of 3rd and 6th months of starting the treatment . Patients were reminded of their follow up visits by a telephone call on the previous day . During the follow up , anthropometric measurements such as weight, height and waist circumference were recorded and fasting blood samples were taken to assess the blood sugar and triglycerides . Patients were given a diary

after enrollment to record the adverse effects and the diary was checked at every follow up visit . Patients were also enquired about the use of concomitant medications through 3 and 6 months .

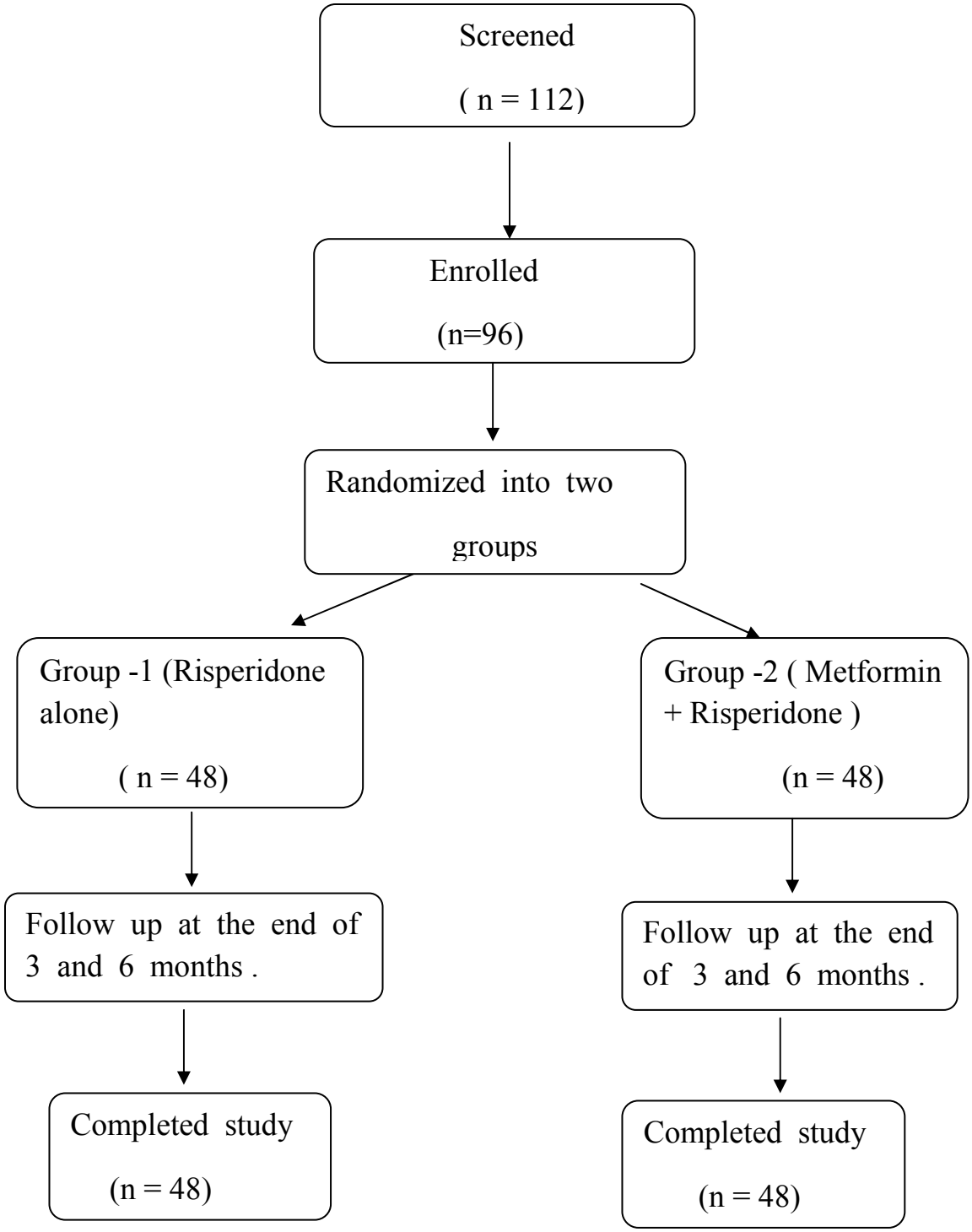
STATISTICAL ANALYSIS :

Statistical analysis was performed with the help of statistical package SPSS (Statistical Package for the Social Sciences) version 11 .

1. Baseline characteristics of both the groups were tabulated by descriptive statistics (mean , standard deviation) and frequency table. They were matched by unpaired student 't' test and Pearson's chi - square test .
2. Between group analysis was done using unpaired student 't' test at baseline , 3 months and 6 months.
3. The student paired 't' test was applied for analysis and interpretation within the group at varied intervals as mentioned above.
4. The categorical variables (BMI staging and development of metabolic syndrome) between two groups were compared by Chi - square test .
5. Adverse events were expressed in percentage .

The p values less than 0.05 ($p<0.05$) was considered as significant in two tailed condition .

PATIENT DISPOSITION : CONSORT DIAGRAM :



RESULTS

For a period of one year from March 2013 to February 2014, around 112 patients newly diagnosed with schizophrenia were initially screened . Based on the inclusion and exclusion criteria , around 96 patients were enrolled for the study. They were randomly assigned through computer generated table into 2 groups receiving either Risperidone alone (or) Metformin along with Risperidone . All the patients completed the study and the results were analyzed .

TABLE - 5

BASELINE CHARACTERISTICS

Baseline parameters		Group 1 (n=48)	Group 2 (n=48)	'p' value
Age (Mean ± SD) yrs		29.69 ± 5.78	28.75 ± 4.56	0.88
Gender n (%)	**Male**	26 (54)	28 (46)	0.68
	Female	22 (46)	20 (54)	
BMI (Mean ±SD)(kg/cm$^{2)}$		22.61 ± 4.03	26.29 ± 4.57	< 0.001
WC (Mean ± SD) cms		84.48 ± 12.17	89.69 ± 13.25	0.04
FBS (Mean ± SD) mg%		90.46 ± 23.47	99.52 ± 30.54	0.1
TGL (Mean ± SD) mg%		146.42 ± 66.26	164.10 ± 81.64	0.25

Table 5 shows the baseline characteristics in both the groups . Baseline characteristics were similar in both the groups ($p>0.05$) except that the patients in group II had higher BMI levels ($p < 0.001$) and larger waist circumference levels ($p = 0.04$) .

TABLE 6

PROPORTION OF PATIENTS DEVELOPING METABOLIC SYNDROME AT THE END OF 6 MONTHS IN BOTH THE GROUPS

Groups	Yes	No	'p' value
Group I	10	38	0.01*
Group II	1	47	

* p value < 0.05 - statistically significant

According to the WHO criteria for metabolic syndrome , it was found that 10 patients in group I developed metabolic syndrome and 1 patient in group II developed metabolic syndrome . The Pearson Chi Square test was used to test the association between the two groups and the p value was found to be < 0.05 implying significant difference between the groups .

TABLE 7

CHANGE IN WAIST CIRCUMFERENCE IN GROUP II PATIENTS (RISPERIDONE +METFORMIN) WITH RESPECT TO BASELINE

Time	Mean	C.I	'p' value
Baseline	89.7	-	-
End of 3 months	89	(-0.9 to -0.4)	< 0.001*
End of 6 months	87.8	(-2.3 to -1.6)	< 0.001*

* p value < 0.05 - statistically significant .

There was a significant reduction in waist circumference at the end of 3 months ($p < 0.001$) and at the end of 6 months ($p < 0.001$) when compared to baseline in group II individuals .

TABLE 8

COMPARISON OF CHANGE IN WAIST CIRCUMFERENCE FROM BASELINE BETWEEN GROUP I AND GROUP II .

Visits	Groups	Mean Difference From Baseline	C.I	'p' value
End of 3 months	**Group I**	2.50	(2.4 to 4)	< 0.001*
	Group II	-0.67		
End of 6 months	**Group I**	3.75	(5 to 6.4)	< 0.001*
	Group II	-1.94		

* p value < 0.05 - statistically significant .

Table 8 shows statistical difference in waist circumference levels between both the groups at the end of 3 months ($p < 0.001$) and at the end of 6 months ($p < 0.001$) .

FIG 5

CHANGES IN WAIST CIRCUMFERENCE IN BOTH THE GROUPS AT THE END OF 3 AND 6 MONTHS .

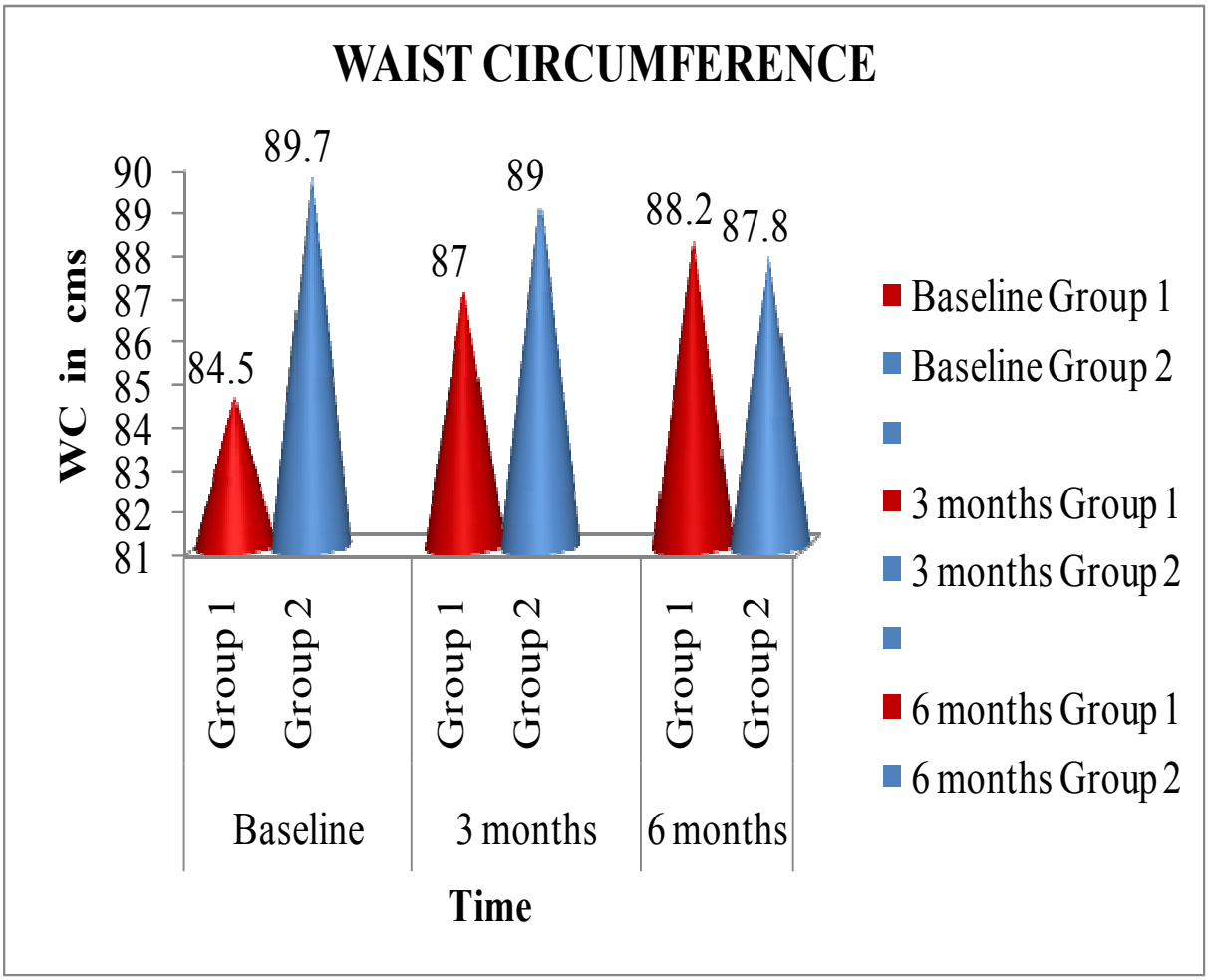


TABLE 9

CHANGE IN BODY MASS INDEX IN GROUP II PATIENTS WITH RESPECT TO BASELINE .

Time	Mean	C . I	'p' value
Baseline	26.3	-	-
End of 3 Months	25.5	(-0.9 to -0.6)	< 0.001*
End of 6 months	24.8	(-1.8 to -1.3)	< 0.001*

* p value < 0.05 - statistically significant .

There was a significant reduction in BMI at the end of 3 months when compared to baseline ($p < 0.001$) in group II individuals. Also the BMI reduction at the end of 6 months with respect to baseline was also statistically significant ($p < 0.001$) .

TABLE 10

COMPARISON OF CHANGE IN BMI FROM BASELINE BETWEEN GROUP I AND GROUP II .

Visits	Groups	Mean Difference From baseline	C.I	'p' value
End of 3 months	**Group 1**	0.99	(1.4 to 2)	< 0.001*
	Group 2	-0.71		
End of 6 months	**Group 1**	1.93	(3.1 to 3.9)	< 0.001*
	Group 2	-1.53		

* p value < 0.05 - statistically significant .

There was a significant statistical difference between both the groups at the end of 3 months ($p < 0.001$) and at the end of 6 months ($p < 0.001$) in BMI .

FIG 6 :

CHANGES IN BMI IN BOTH THE GROUPS AT THE END OF 3 AND 6 MONTHS .

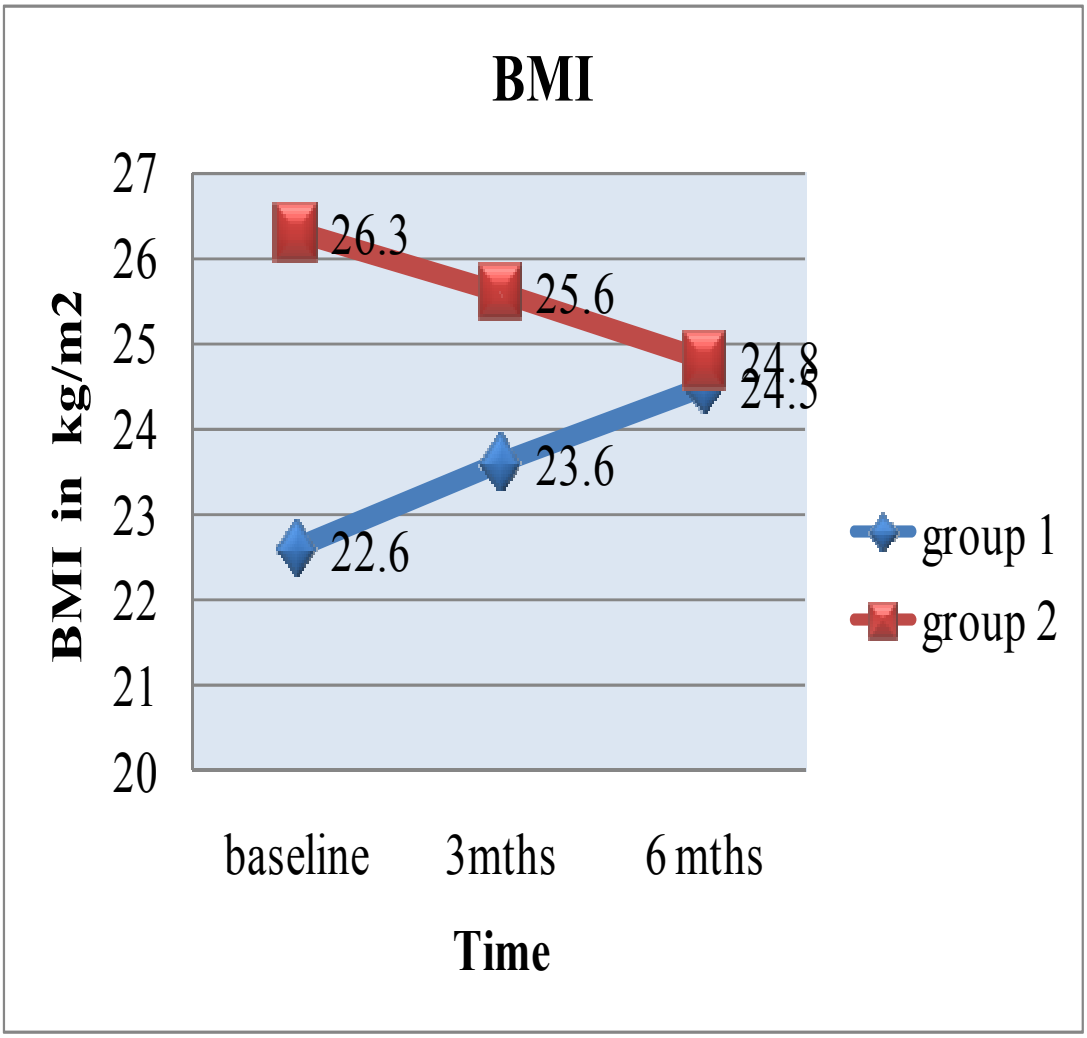


TABLE 11

PROPORTION OF PATIENTS PROGRESSED TO A STAGE HIGHER FROM THE BASELINE IN TERMS OF BMI AT THE END OF 3 MONTHS .

Proportions of patients			'p' value
Groups	**Yes**	**No**	
Group 1	8	40	0.003*
Group 2	Nil	48	

* p value < 0.05 , statistically significant .

Table 11 shows the proportion of patients who progressed a stage higher from baseline in terms of BMI , 3 months after treatment . When compared to group I , significantly lesser proportion of patients in group II progressed to the next stage . The Pearson Chi Square test was used to test the association between the two groups and the p value was found to be < 0.05 implying significant difference between the groups .

TABLE 12

CHANGE IN FASTING BLOOD SUGAR LEVELS IN GROUP II PATIENTS WITH RESPECT TO BASELINE

Time	Mean	C.I	'p' value
Baseline	99.5	-	-
End of 3 months	102	(-2 to 7.1)	0.28
End of 6 Months	94	(-10 to -1.3)	$< 0.001^{*}$

* p value < 0.05 - statistically significant .

Table 12 demonstrates a significant reduction in FBS levels at the end of 6 months of treatment ($p < 0.001$) in group II individuals .

TABLE 13

COMPARISON OF CHANGE IN FASTING BLOOD SUGAR LEVELS FROM BASELINE BETWEEN GROUP I AND GROUP II .

Visits	Groups	Mean Difference From baseline	C.I	'p' value
End of 3 months	Group 1	15.81	(6.3 to 20.3)	< 0.001*
	Group 2	2.52		
End of 6 months	Group 1	28.04	(26.3 to 41)	< 0.001*
	Group 2	-5.58		

* p value < 0.05 - statistically significant .

Table 13 shows statistical difference in FBS levels between both the groups at the end of 3 months ($p < 0.001$) and at the end of 6 months of treatment ($p < 0.001$) .

FIG 7

CHANGES IN FBS LEVELS IN BOTH THE GROUPS AT THE END OF 3 AND 6 MONTHS

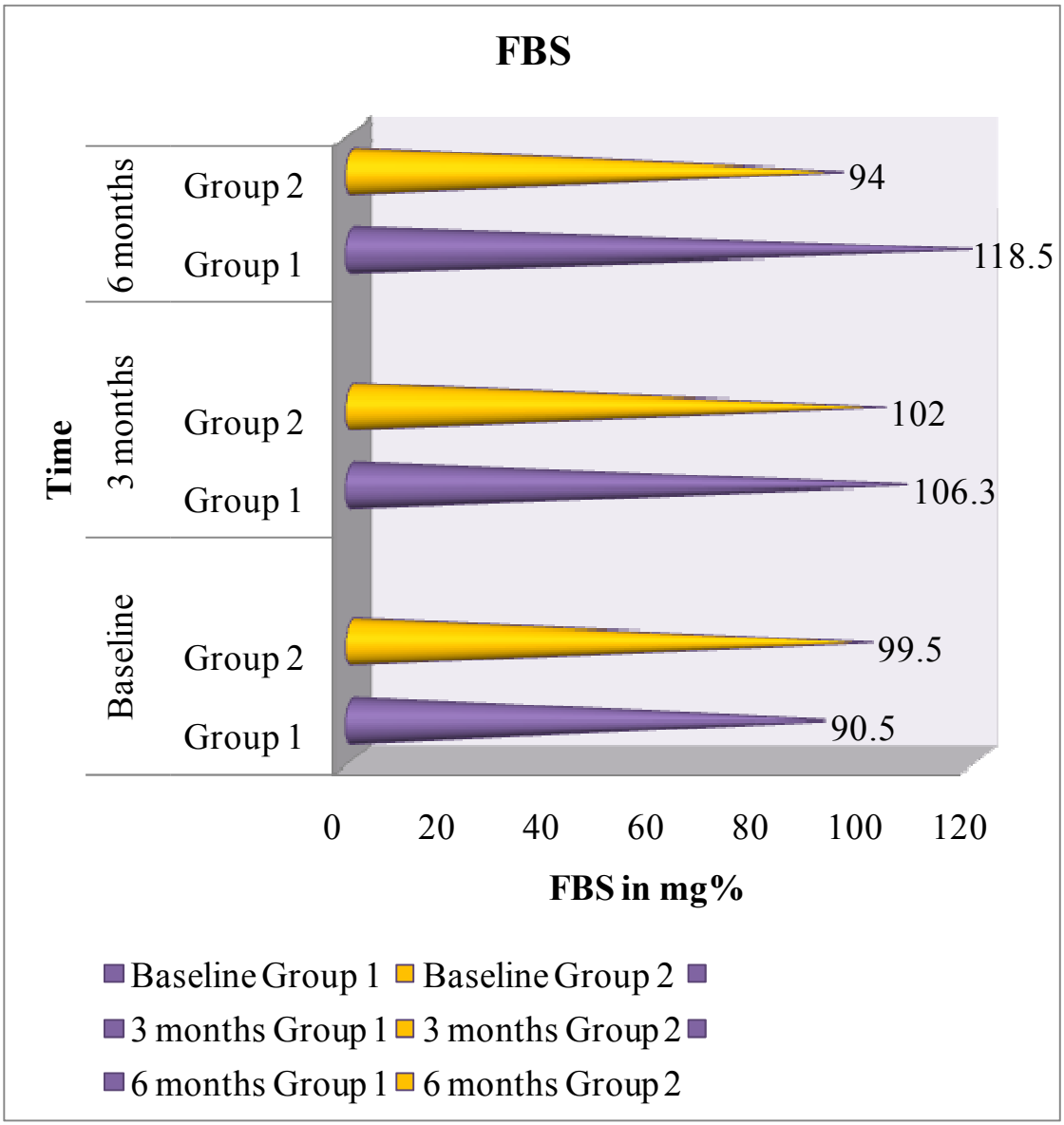


TABLE 14

CHANGE IN FASTING TRIGLYCERIDE LEVELS IN GROUP II PATIENTS WITH RESPECT TO BASELINE

Time	Mean	C.I	'p' value
Baseline	164.1	-	-
End of 3 Months	161.5	(-10 to 4.8)	0.49
End of 6 Months	150.3	(-19.8 to -7.7)	< 0.001*

* p value < 0.05 - statistically significant .

Table 14 demonstrates no significant changes in TGL levels at the end of 3 months ($p = 0.49$) with respect to baseline in Metformin group . However there was a significant reduction in TGL levels at the end of 6 months ($p < 0.001$) in group II individuals .

TABLE 15

COMPARISON OF CHANGE IN FASTING TRIGLYCERIDE LEVELS FROM BASELINE BETWEEN GROUP I AND GROUP II

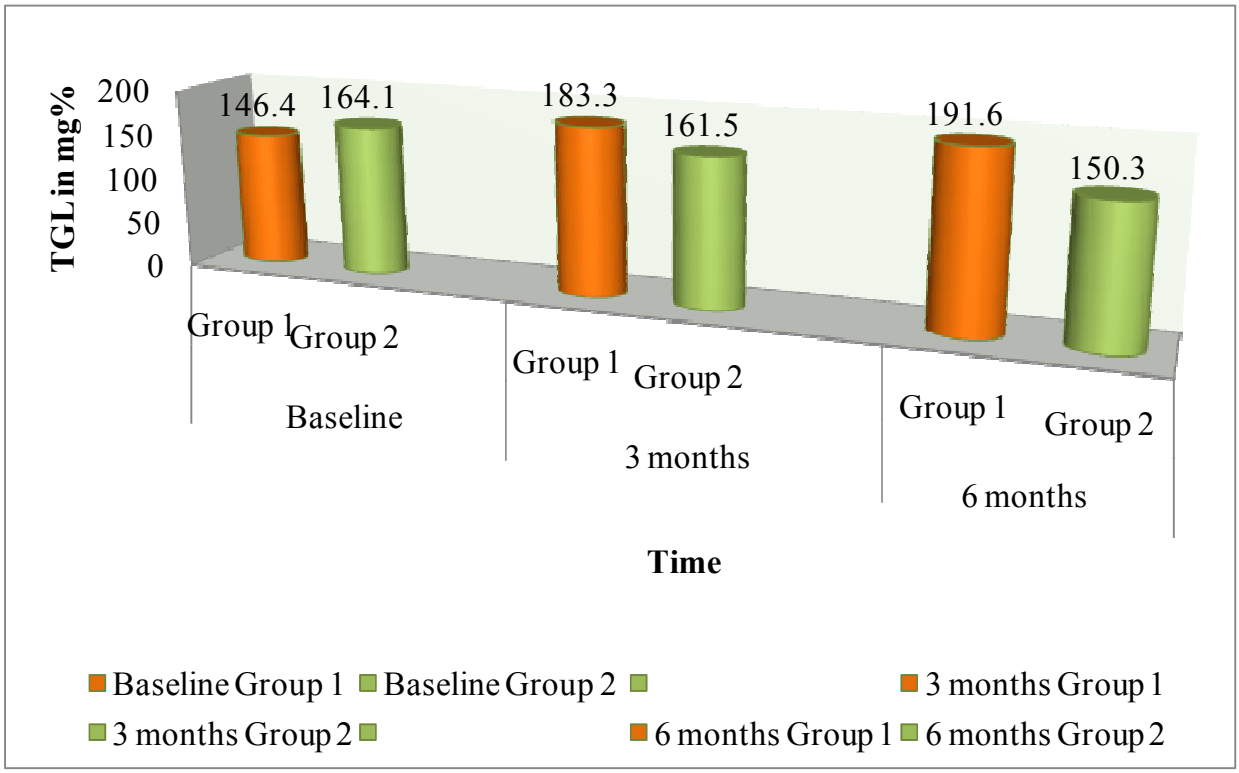
Visits	Groups	Mean Difference From Baseline	C.I	'p' value
End of 3 Months	Group 1	36.83	(22 to 57.1)	< 0.001*
	Group 2	-2.58		
End of 6 months	Group 1	45.21	(43 to 75.1)	< 0.001*
	Group 2	-13.77		

* p value < 0.05 - statistically significant .

Table 15 shows significant rise in TGL levels at the end of 6 months compared to baseline in group I individuals and similarly Metformin along with Risperidone has significantly caused reduction in TGL levels at the end of 6 months in group II individuals signifying the existence of statistical difference between both the groups .

FIG 8

CHANGES IN TGL LEVELS IN BOTH THE GROUPS AT THE END OF 3 AND 6 MONTHS



Adverse effects :

Metformin was tolerated well by the study participants .The treatment emergent adverse effects with Metformin were mainly gastrointestinal side effects such as diarrhea and gastritis . They were reported by 5% of patients and were transient . It did not lead to the discontinuation of the drug . There were no reports suggestive of lactic acidosis (or) hypoglycemia .

Discussion :

Schizophrenia is considered the prototypic disorder for understanding the phenomenology of psychosis [3] . It is associated with a high morbidity and mortality resulting from strikingly high suicide rate of 10 %[4]. Atypical antipsychotics are commonly used for managing schizophrenia spectrum disorders nowadays . However their benefit - to - risk ratio is challenged by metabolic abnormalities and weight gain[82] . Individuals suffering from both psychotic illness and obesity encounter the dual stigma and discrimination that contributes to poor self esteem and psychological distress and may impact medication compliance thereby leading to relapse[121] .

Adherence to medications is difficult and also physical interventions may not be possible in psychiatric patients . Net weight loss in chronic patients who have undergone indeterminate weight gain seems to be more difficult . But weight gain mitigation at early stages of treatment seems to be more easier and clinically advantageous . Adverse cardio metabolic effects of atypical antipsychotics may be minimized by several strategies such as a) healthy lifestyle intervention[122], b) switching to lower risk antipsychotics[123] and c) the addition of medication that may reduce body weight and / (or) lipid and glucose parameters[124].

Metformin has a well established safety profile in both adolescents and young adults in contrast to the other weight reducing drugs which have potential serious adverse effects. Importantly Metformin is not metabolised by hepatic P_{450} enzymes. Hence significant drug - drug interactions are not reported. Also there exists no specific interactions with antipsychotic medication[125]. Hence the present study was aimed to evaluate the effectiveness and safety of Metformin along with Risperidone in preventing the occurence of antipsychotic - induced Metabolic syndrome in first episode schizophrenia patients .

As the prevalence of metabolic syndrome per se is common after 40 years , we conducted the study only in adolescents and young adults (18 to 40 years). The mean age in group I (Risperidone alone) was (29.69 ± 5.78) years and that in group II (Metformin + Risperidone) was (28.75 ± 4.56) years. In our study , baseline characteristics were similar in both the groups ($p > 0.05$) except that the patients in group II had higher BMI levels ($p < 0.001$) and larger waist circumference levels ($p = 0.04$) .

With regard to the primary endpoint, the development of metabolic syndrome was assessed in both the group of patients using the WHO criteria for metabolic syndrome . 10 patients (21%) in group I and 1 patient (2%) in group II developed metabolic syndrome thereby

implying that Metformin seems to be effective in reducing the incidence of metabolic syndrome .

The secondary endpoints in our study were the individual components of metabolic syndrome (Changes in WC , BMI , FBS and TGL). Waist circumference has better correlation with abdominal fat and is strongly associated with cardiovascular risk factors when compared to other parameters[126] . Increase in waist circumference of every 2 inches is associated with an increase in mortality by 17% in men and 13% increase in women .

Recent studies suggest that the ability of subcutaneous fat depots to store excess energy is limited . This results in an "overflow" of excess energy to 'ectopic sites' such as skeletal muscle and liver and intra abdominal adipose tissue . This excessive ectopic fat eventually leads to metabolic dysfunction in organs and so increase in intra myocellular fat is found to be associated with skeletal muscle insulin resistance[127] and increase in intrahepatic fat is associated with hepatic insulin resistance[128.]

Metformin suppresses appetite and causes satiety through an increase in insulin sensitivity and reduction in hyperinsulinemia . GLP - 1 (incretin) released from L cells in intestine via glucose dependent insulin secretion lowers blood glucose levels and promotes satiety by slowing gastric emptying . In a study by Mannuci et al , it was found

that the reduced intake of food and weight loss in Metformin treated subjects might be related to the increase in GLP-1 levels[129] .

In our study , within the group , group II showed mean waist reduction of (-1.9 cms) from the baseline at the end of 6 months . This implies that waist circumference reduction by Metformin will have positive impact in preventing metabolic syndrome .

Waist circumference is a marker of central obesity , whereas BMI is a measure of overall adiposity[126] . BMI is strongly associated with cardiovascular mortality which is partially due to the effect of obesity on lipoprotein metabolism , blood pressure and insulin resistance[130] . However cardiovascular disease is better predicted with BMI coupled together with WC than with the BMI alone[131] . In our study , mean baseline BMI value got reduced from 26.29 to 25.5 at 3 months and 24.8 at 6 months of treatment. These results were similar to the study done in USA by Morrison et al which demonstrated significant (2.22 kg/m^2) reduction in BMI with Metformin in children taking Risperidone , Olanzapine , Quetiapine (or) Valproate[132] . Hence both BMI and WC play a crucial role in the assessment of metabolic syndrome[126] and metformin along with Risperidone has been found to decrease both waist circumference and BMI suggesting its importance in the prevention of metabolic syndrome .

As we all know about the microvascular and macrovascular complications associated with long term hyperglycemia , normalization of fasting blood sugar levels at the earliest is considered wise in the prevention of metabolic syndrome . Metformin reduces fasting blood sugar levels by increasing the peripheral utilisation of glucose[10] . In our study , fasting blood sugar levels did not show any statistical difference at 3 months of treatment (p=0.28) which was comparable to the results of the study by Carrizo et al that interpreted that Metformin had no significant effect on fasting BSL compared with placebo at 14 weeks of treatment[133] . But in our study at 6 months of treatment , there was a significant reduction in fasting BSL (p <0.001) . This result was similar to the double - blind , placebo controlled study conducted by Baptista et al showing significant fasting BSL reduction after Metformin addition (p=0.02)[120] .

Elevated triglycerides along with increased waist cicrumference is termed as hypertriglyceridemic waist which is found to have association with arteriographic CVD[134] . Also TG elevation is found associated with stroke and MI risk in NHANES III[135] . Metformin increases AMPK and hormone sensitive lipase activities in brown adipose tissue thereby lowering TGL by enhancing uptake of VLDL - TGL , lipolysis of intracellular TGL and subsequent fatty acid oxidation by mitochondria[136] .

In our study , fasting triglyceride levels did not differ statistically at 3 months when compared to baseline ($p=0.49$) in group II individuals . However the mean triglyceride level (164.1 mg%) at baseline dropped down (150.3 mg%) at 6 months suggesting there was significant statistical difference at 6 months ($p<0.001$) . This result was similar to the study conducted by Shin et al which showed significant reduction in triglyceride levels after 12 weeks of treatment with Metformin[137] .

Thus our study has shown that Metformin is effective and safe in preventing the occurence of antipsychotic induced metabolic syndrome in adolescents and young adults with first episode schizophrenia.

Our study has some limitations . First , as the duration of study is only 6 months , we do not know whether the improved BMI, WC, FBG and TGL levels could be sustained .

Second , all our study participants were cared by their caregivers (or) parents and hence they could have better adherence with Metformin when compared to patients living independently with schizophrenia .

Hence due to the feasibility of Risperidone and Metformin in our hospital setting and due to the paucity of trials using both these drugs , we conducted this study using Metformin and Risperidone . Further studies with more number of patients , long term follow up

and Metformin along with lifestyle intervention would provide more appealing results regarding the efficacy and safety of Metformin for the prevention of antipsychotic induced metabolic syndrome .

CONCLUSION

- ✓ To conclude, the use of Metformin along with Risperidone is safe and effective in the prevention of metabolic syndrome induced by atypical antipsychotics .
- ✓ This may have a good impact on the long term cardiovascular morbidity and mortality of the schizophrenia patients .

APPENDIX (i)

ABBREVIATIONS

AACE	:American Association of Clinical Endocrinology
ACEI	:Angiotensin Converting Enzyme Inhibitor
AHA	:American Heart Association
AMPK	:AMP dependent Protein Kinase
BMI	:Body Mass Index
BSL	:Blood Sugar Level
CATIE study	:Clinical Antipsychotic Trials of Intervention Effectiveness study
CTZ	:Chemoreceptor Trigger Zone
CUtLASS	:Cost Utility of Latest Antipsychotic drugs in schizophrenia Study
DALY	: Disability Adjusted Life Years
DLPFC	: Dorsolateral Prefrontal Cortex
DSM	: Diagnostic and Statistical Manual of Mental disorders
ECT	: Electro Convulsive Therapy
EGIR	: European Group for the study of Insulin Resistance
EPS	: Extrapyramidal side effects
FBS	: Fasting Blood Sugar
HAART	: Highly Active Anti Retroviral Therapy
ICD	: International Classification of Diseases
IDF	: International Diabetes Federation
LAI	: Long acting Injectables

MetS : Metabolic syndrome

NCEP:ATPIII : National Cholesterol Education Program : Adult Treatment Panel III

NHANES III : National Health And Nutrition Examination Survey III

NHLBI : National Heart,Lung and Blood Institute

NIMH : National Institute of Mental Health

RDC : Research Diagnostic criteria

TGL : Triglycerides

VMPFC : Ventromedial Prefrontal Cortex

WC : Waist Circumference

நோயாளிகளுக்கு அறிவிப்பு மற்றும் ஒப்புதல் படிவம்

மருத்துவ ஆய்வில் பங்கேற்பதற்கு

ஆய்வு செய்யப்படும் தலைப்பு **: ஏடிப்பிக்கல் ஏண்டி சைகாடிக் மருந்தினால் உண்டாகும் வளர்சிதை மாற்ற நோய்குறியை தடுக்கும் பொருட்டு மெட்பார்மின் அளித்து ஒரு ஆய்வு.**

பங்கு பெறுபவரின் பெயர் **:**

பங்கு பெறுபவரின் வயது **:**

		பங்கு பெறுபவர் இதனை குறிக்கவும்
1.	நான் மேலே குறிப்பிட்டுள்ள மருத்து ஆய்வின் விவரங்களை நான் படித்து புரிந்து கொண்டேன். என்னுடைய சந்தேகங்களை கேட்கவும், அதற்கான தகுந்த விளக்கங்களை பெறவும் வாய்ப்பளிக்கப்பட்டுள்ளது என அறிந்து கொண்டேன்.	☐
2.	நான் இவ்வாய்வில் தன்னிச்சையாக தான் பங்கேற்கிறேன். எந்த காரணத்தினாலோ எந்த கட்டத்திலும், எந்த சட்ட சிக்கலும் உட்படாமல் நான் இவ்வாய்வில் இருந்து விலகி கொள்ளலாம் என்றும் அறிந்து கொண்டேன்.	☐
3.	இந்த ஆய்வு சம்பந்தமாகவோ, இதைச் சார்ந்து மேலும் ஆய்வு மேற்கொள்ளும் போதும் இந்த ஆய்வில் பங்கு பெறும் மருத்துவர் என்னுடைய மருத்துவ அறிக்கையை பார்ப்பதற்கு கொள்கிறேன். நான் ஆய்வில் இருந்து விலகிக் கொண்டாலும் இது பொருந்தும் என அறிகிறேன்.	☐
4.	இந்த ஆய்வின் மூலம் கிடைக்கும் தகவலையோ, முடிவையோ பயன்படுத்திக் கொள்ள மறுக்க மாட்டேன்.	☐
5.	இந்த ஆய்வில் பங்கு கொள்ள ஒப்புக் கொள்கிறேன். எனக்கு கொடுக்கப்பட்ட அறிவுரைகளின் படி நடந்து கொள்வதுடன் ஆய்வை மேற்கொள்ளும் மருந்து அணிக்கு உண்மையுடன் இருப்பேன் என உறுதியளிக்கிறேன். என் உடல் நலம் பாதிக்கப்பட்டாலோ, அல்லது எதிர்பாராக வழக்கத்திற்கு மாறான நோய்குறி தென்பட்டாலோ உடனே இதை மருத்துவ அணியிடம் தெரிவிப்பேன் என உறுதி அளிக்கிறேன்.	☐

பங்கேற்பவரின் கையொப்பம்/ _____இடம் _____ தேதி _____

பங்கேற்பவரின் பெயர் மற்றும் விலாசம்

ஆய்வாளரின் கையொப்பம்/ _____இடம் _____ தேதி _____

மையம் _____

கல்வியறிவு இல்லாதவர்க்கு (கைரேகை வைத்தவர்களுக்கு)இது அவசியம் தேவை

சாட்சியின் கையொப்பம்/ _____இடம் _____ தேதி _____

பெயர் மற்றும் விலாசம் _____

INFORMED CONSENT FORM

Study Title : A Randomized, Open Labelled, Single Centered Study Of Metformin In Preventing Metabolic Syndrome Associated With Initiation Of Atypical Antipsychotic Therapy In Adolescents And Young Adults

StudyNumber_____
Subject's Full Name _____
Date of Birth/Age_____
Address
_____
_____

1. I confirm that I have read and understood the information sheet dated for the above study and have had the opportunity to ask questions. **or** I have been explained the nature of the study by the Investigator and had the opportunity to ask questions
2. I understand that my participation in the study is voluntary and that I am free to withdraw at anytime, without giving any reason and without my medical care or legal rights being affected.
3. I understand that the sponsor of the clinical trial/project, others working on the Sponsor's behalf,the Ethics Committee and the regulatory authorities will not need my permission to look at my health records both in respect of the current study and any further research that may be conducted in relation to it, even if I withdraw from the trial. However, I understand that my Identity will not be revealed in any information released to third parties or published.
4. I agree not to restrict the use of any data or results that arise from this study provided such a use isonly for scientific purpose(s)
5. I agree to take part in the above study

Signature (or Thumb impression) of the Subject/Legally Acceptable Representative: _____
Signatory's Name _____
Date _____
Signature of the Investigator _____
Date _____
Study Investigator's Name _____
Signature of the Witness _____ Date _____
Name of the Witness

APPENDIX (iii)

STUDY PROFORMA

NAME : **AGE/SEX :**

ADDRESS :

CONTACT NUMBER :

H/O :

TAKING TREATMENT SINCE :

GENERAL EXAMINATION :

BP : **PULSE RATE :**

CVS :

RS :

ABDOMEN :

CNS :

INVESTIGATIONS DURING SCREENING :

a) <u>Anthropometric measurements</u> :

- ❖ Height
- ❖ Weight
- ❖ Waist circumference

b<u>) Blood investigations</u> :

- ❖ Complete blood count
- ❖ Fasting blood sugar
- ❖ Serum urea
- ❖ Serum creatinine

- ❖ Liver function tests
- ❖ Routine urine analysis
- ❖ Fasting lipid profile .

PARAMETERS ASSESSED :

	BASELINE	END OF 3 MONTHS	END OF 6 MONTHS
WEIGHT			
HEIGHT			
BODY MASS INDEX			
WAIST CICUMFERENCE			
FASTING BLOOD GLUCOSE			
FASTING TRIGLYCERIDES			

GROUP I (RISPERIDONE ALONE)																
GROUP	S.NO	AGE	SEX M-1,F-2	BODY MASS INDEX			WAIST CIRCUM (IN CMS)			FASTING BS ING BS (IN GM/DL)			TGL (IN MG%)		
				BASELINE	3 MTHS	6 MTHS	BASELINE	3 MTHS	6 MTHS	BASELINE	3 MTHS	6 MTHS	BASELINE	3 MTHS	6 MTHS
1	1	26	1	22.1	22.3	23.6	82	82	84	90	92	100	132	141	156
1	2	34	2	21.8	22.9	24.08	80	89	90	68	87	86	185	139	360
1	3	19	1	21.5	22.9	24.4	129	130	132	143	149	156	77	90	110
1	4	40	1	22.9	25.7	27	94	95	98	100	108	115	251	261	245
1	5	25	1	22.2	22.5	23.2	95	97	100	81	101	98	116	136	129
1	6	23	1	22.5	22.9	23.6	85	85	86	83	131	142	90	120	126
1	7	34	1	23.9	24.2	24.9	82	83	84	86	111	126	157	168	179
1	8	40	2	19.5	20.8	22.5	75	75	76	86	98	110	123	136	148
1	9	33	2	27.7	28.1	29	98	99	99	76	110	138	119	156	178
1	10	21	2	21.8	22.7	23.6	98	99	101	83	126	141	42	78	96
1	11	30	2	24.6	25.4	26.3	78	79	80	60	121	117	76	118	127
1	12	37	2	21.6	21.6	22.4	73	77	80	92	100	108	156	225	240
1	13	28	2	23.6	24.5	25.3	84	87	89	84	98	121	71	101	152
1	14	30	2	22.6	23	23.7	84	86	86	101	103	98	282	285	296
1	15	28	1	22.3	23.4	24.5	75	78	80	96	110	121	88	96	128
1	16	39	2	17.3	18.6	20.2	79	82	90	88	95	112	123	146	151
1	17	35	1	26.2	26.6	27.6	93	102	98	79	139	149	111	266	260
1	18	33	2	34.2	35.2	36.2	95	98	101	99	101	108	86	92	112
1	19	33	1	18.1	18.5	18.1	72	84	79	109	126	148	197	290	121
1	20	24	2	23.7	25.9	25	75	78	80	142	113	105	100	239	100
1	21	30	2	16.9	17.8	20	67	69	71	96	112	126	107	125	138
1	22	40	2	29.3	29.7	30.5	93	96	97	95	98	100	94	126	134
1	23	33	1	26.7	27	27.4	101	105	104	102	116	122	137	151	146
1	24	35	2	23.5	24.4	25.3	81	83	83	102	112	110	225	236	251
1	25	39	1	17.5	18.3	19.4	87	88	90	134	146	140	156	181	178
1	26	29	2	19	19.9	20.8	65	67	68	79	96	110	123	161	158
1	27	32	2	31.2	32	32.9	97	98	99	69	71	86	142	156	176
1	28	30	1	29.4	29.8	30.5	98	98	100	187	182	175	197	212	201
1	29	34	1	25.4	25.4	26.6	86	95	94	108	121	135	88	105	123
1	30	32	1	19.5	21.5	23.4	72	78	80	66	78	80	79	86	116
1	31	20	1	24.3	25.2	26.4	78	83	82	87	96	101	248	251	245
1	32	24	1	22.5	22.9	23.7	79	80	80	62	78	88	58	66	97
1	33	36	2	29.5	32	32.9	105	108	112	85	108	124	180	470	387
1	34	31	2	25.6	24.3	25.6	94	95	95	89	150	142	182	220	227
1	35	20	1	21.5	22.1	22.8	87	88	89	61	64	75	72	95	87
1	36	31	2	27.5	28.8	29.7	104	102	105	74	82	95	377	390	416
1	37	20	2	17.8	19.6	21.3	65	69	70	68	77	110	224	337	326
1	38	26	1	19.5	20.3	21.1	72	74	75	106	67	126	155	160	180
1	39	32	1	17.6	18.8	20	72	73	73	97	119	132	132	149	168
1	40	31	1	24.7	27.9	28.8	92	92	94	65	87	118	137	322	357
1	41	23	1	20	20.7	21.4	77	78	80	94	126	145	220	255	273
1	42	28	1	21.8	22.5	23.2	80	82	84	98	113	136	156	172	194
1	43	27	1	18.4	19	19.7	78	79	81	90	113	126	150	168	187
1	44	26	1	21.2	24	24.8	81	84	86	68	73	108	143	166	182
1	45	28	1	20.4	23.7	24.7	86	88	89	70	96	108	178	186	201
1	46	25	2	18.7	19.1	19.8	78	80	81	87	98	118	151	188	196
1	47	30	2	15.6	16.9	18.2	74	76	77	81	95	121	81	138	179
1	48	21	1	20.2	21.3	22	80	82	83	76	108	132	254	241	261

GROUP II (RISPERIDONE + METFORMIN)															
					BODY MASS INDEX		WAIST CIRCUM (IN CMS)			FASTING BS (IN MG%)			TGL (IN MG%)		
GROUP	S.NO	AGE	SEX M-1 , F-2	BASELINE	3 MTHS	6 MTHS	BASELINE	3 MTHS	6 MTHS	BASELINE	3 MTHS	6 MTHS	BASELINE	3 MTHS	6 MTHS
2	1	32	1	22.8	22.4	22.1	85	85	84	101	118	96	161	150	136
2	2	25	1	25.3	24.4	23.1	87	0	86	118	116	86	88	100	98
2	3	30	2	27.9	26.3	24.2	92	91	90	128	119	96	104	98	95
2	4	27	1	22.6	23.7	21.8	86	86	85	73	93	86	96	168	127
2	5	33	2	34	34	33.6	120	120	118	81	155	92	70	168	104
2	6	26	1	22.3	21.9	21.5	68	68	67	71	86	91	125	132	112
2	7	31	1	27.3	26.6	25.8	92	92	90	80	85	76	185	172	161
2	8	33	1	23.6	23.6	22.9	72	72	71	109	112	96	197	195	174
2	9	20	1	24.6	24.1	23.3	73	73	72	61	72	65	157	161	145
2	10	35	1	24.4	23.6	22.9	88	88	87	116	118	110	144	152	142
2	11	31	2	22.7	22.2	21.8	91	90	90	127	123	112	156	158	143
2	12	18	1	24.2	22.8	22.1	89	86	83	83	74	75	94	87	85
2	13	35	1	23.8	22.9	22.5	73	73	72	52	78	60	105	112	106
2	14	29	2	32.9	31.6	30.3	105	103	102	151	145	143	425	386	372
2	15	22	1	27.4	26.2	25.1	74	74	73	67	75	72	90	98	93
2	16	26	1	25.8	24.8	24.4	90	90	89	60	72	68	243	236	220
2	17	31	1	25.4	24.6	23.8	67	67	66	123	121	109	157	152	145
2	18	24	1	22.1	21.1	20.8	80	80	78	60	72	65	130	127	112
2	19	38	2	31.9	30.4	28.5	109	107	105	128	118	96	178	156	158
2	20	32	1	25	24.6	23.9	81	80	78	152	145	136	148	132	128
2	21	29	2	25.3	24.5	23.6	105	105	104	124	114	96	110	126	107
2	22	25	1	25.9	25.1	24.4	97	96	96	196	175	168	184	177	172
2	23	24	1	25.1	24.8	24.4	88	87	86	163	155	148	156	145	142
2	24	30	1	24.2	23.8	22.3	80	79	78	118	92	89	188	139	142
2	25	30	2	28.2	27.1	26.3	101	100	99	79	85	99	172	165	158
2	26	32	1	24.2	23.8	23.8	92	91	91	93	100	95	132	142	128
2	27	32	2	42.8	42.3	39.2	119	119	118	109	89	98	110	130	126
2	28	29	1	24.3	23.9	23.1	86	87	86	78	84	82	148	136	142
2	29	23	2	30.9	30	28.5	96	95	95	112	101	100	73	86	91
2	30	34	1	25.1	24.2	23.4	91	90	90	74	89	92	515	458	465
2	31	23	1	24.4	24	23.7	74	73	71	66	78	85	88	82	90
2	32	25	2	25	24.6	24.6	79	78	77	121	112	110	127	132	112
2	33	30	2	22.8	22.4	22.4	94	93	90	82	95	101	134	142	126
2	34	28	2	23.9	23.5	23.1	88	87	85	76	85	80	277	243	212
2	35	23	2	21.2	20.8	20.8	83	82	80	137	121	118	111	126	116
2	36	25	1	22.3	21.9	21.6	81	80	78	75	83	68	87	109	94
2	37	26	2	41.6	39.5	37.5	113	112	110	101	96	98	203	198	176
2	38	28	1	24.6	24.1	23.3	72	71	70	81	97	78	179	168	165
2	39	22	1	22.8	21.8	21.3	88	87	85	79	87	76	114	126	118
2	40	27	2	21.5	21	20.5	85	85	84	84	96	78	276	255	221
2	41	30	2	28.6	27.7	26.3	100	98	97	93	81	85	176	143	158
2	42	34	1	32.7	31.6	30.9	111	109	109	107	98	95	246	230	210
2	43	35	2	28.8	27.9	26.7	107	107	105	79	78	65	187	162	145
2	44	33	2	27	26.2	25.4	108	107	105	127	113	96	186	165	151
2	45	30	2	30.5	29.6	28.7	100	98	97	112	108	101	194	182	170
2	46	29	1	23.5	23.1	22.8	85	85	83	71	85	82	166	153	155
2	47	28	1	25.7	24.9	24.5	74	74	72	116	110	107	167	155	142
2	48	38	2	23.1	22.1	21.1	86	86	85	83	94	89	118	138	126

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